

COMPOSITIONS AND METHODS FOR INHIBITING *LPA* EXPRESSION

TECHNICAL FIELD

[0001] The disclosure relates to oligonucleotides that inhibit apolipoprotein(a) ("*LPA*") expression and uses thereof, particularly uses relating to treating diseases, disorders and/or conditions associated with *LPA* expression.

REFERENCE TO SEQUENCE LISTING

[0002] A Sequence Listing is submitted concurrently with the specification as an ASCII formatted text file, with a file name of DRNA_C002WO_ST25.txt, a creation date of August 5, 2021, and a size of 238 kilobytes. The information in the electronic format of the Sequence Listing is part of the specification and is hereby incorporated herein by reference in its entirety.

BACKGROUND

[0003] 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.

[0004] Therefore, there exists a need for therapeutics and treatments related to these and other *LPA*- related diseases.

BRIEF SUMMARY OF THE INVENTION

[0005] Embodiments of the disclosure relate to compositions and methods for treating a disease, disorder and/or condition related to *LPA* expression. The disclosure is based, in part, on the discovery and development of oligonucleotides that selectively inhibit and/or reduce *LPA* expression in the liver. Accordingly, target sequences within *LPA* mRNA were identified and RNAi oligonucleotides that bind to these target sequences and inhibit *LPA* mRNA expression were generated. As demonstrated herein, the RNAi oligonucleotides inhibited monkey and human *LPA* expression in the liver. Without being bound by theory, the RNAi oligonucleotides described herein are useful for treating a disease, disorder or condition associated with *LPA* expression (*e.g.*, cardiometabolic diseases, atherosclerosis, dyslipidemia, NAFLD and NASH).

[0006] Accordingly, in some embodiments, the present disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0007] In any of the foregoing or related embodiments, the sense strand is 15 to 50 nucleotides in length. In some embodiments, the sense strand is 18 to 36 nucleotides in length.

[0008] In any of the foregoing or related aspects, the antisense strand is 15 to 30 nucleotides in length.

[0009] In any of the foregoing or related aspects, the antisense strand is 22 nucleotides in length and wherein antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length.

[0010] In any of the foregoing or related aspects, the region of complementarity is at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.

[0011] In any of the foregoing or related aspects, the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length.

[0012] In some aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0013] In other aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0014] In yet other aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0015] In further aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0016] In other aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0017] In some aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0018] In other aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0019] In yet other aspects, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

[0020] In any of the foregoing or related aspects, L is a triloop or a tetraloop. In some embodiments, L is a tetraloop. In some embodiments, the tetraloop comprises the sequence 5'-GAAA-3'.

[0021] In any of the foregoing or related embodiments, the S1 and S2 are 1-10 nucleotides in length and have the same length. In some embodiments, S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length. In some embodiments, S1 and S2 are 6 nucleotides in length. In some embodiments, the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1197).

[0022] In any of the foregoing or related embodiments, the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length. In some embodiments, the 3' overhang sequence is 2 nucleotides in length, optionally wherein the 3' overhang sequence is GG.

[0023] In any of the foregoing or related embodiments, the oligonucleotide comprises at least one modified nucleotide. In some embodiments, the modified nucleotide comprises a 2'-modification. In some embodiments, the 2'-modification is a modification selected from 2'-

aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid. In some embodiments, all nucleotides comprising the oligonucleotide are modified, optionally wherein the modification is a 2'-modification selected from 2'-fluoro and 2'-O-methyl.

[0024] In any of the foregoing or related embodiments, the oligonucleotide comprises at least one modified internucleotide linkage. In some embodiments, the at least one modified internucleotide linkage is a phosphorothioate linkage.

[0025] In any of the foregoing or related embodiments, the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog. In some embodiments, the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonyl phosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.

[0026] In any of the foregoing or related embodiments, at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands. In some embodiments, each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid. In some embodiments, each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety. In some embodiments, the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety. In some embodiments, up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

[0027] In any of the foregoing or related embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, and 403.

[0028] In any of the foregoing or related embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, and 803.

[0029] In any of the foregoing or related embodiments, the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 393 and 793, respectively;
- (b) SEQ ID NOs: 388 and 788, respectively;
- (c) SEQ ID NOs: 389 and 789, respectively;
- (d) SEQ ID NOs: 390 and 790, respectively;
- (e) SEQ ID NOs: 391 and 791, respectively;

- (f) SEQ ID NOs: 392 and 792, respectively;
- (g) SEQ ID NOs: 394 and 794, respectively;
- (h) SEQ ID NOs: 395 and 795, respectively;
- (i) SEQ ID NOs: 396 and 796, respectively;
- (j) SEQ ID NOs: 397 and 797, respectively;
- (k) SEQ ID NOs: 398 and 798, respectively;
- (l) SEQ ID NOs: 399 and 799, respectively;
- (m) SEQ ID NOs: 400 and 800, respectively;
- (n) SEQ ID NOs: 401 and 801, respectively;
- (o) SEQ ID NOs: 402 and 802, respectively; and
- (p) SEQ ID NOs: 403 and 803, respectively.

[0030] In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 393, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 793. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 388, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 788. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 389, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 789. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 390, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 790. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 391, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 791. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 392, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 394, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 794. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 395, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 795. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 396, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 796. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 397, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 797. In some embodiments, the sense strand comprises

a nucleotide sequence as set forth in SEQ ID NO: 398, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 798. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 399, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 799. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 400, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 800. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 401, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 801. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 402, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 802. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 403, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 803.

[0031] In some embodiments, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0032] In further embodiments, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0033] In other embodiments, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of

any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0034] In some embodiments, the disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise one or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0035] In some embodiments, the disclosure provides a method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of the RNAi oligonucleotide of any one of the preceding claims, or pharmaceutical composition thereof, thereby treating the subject.

[0036] In other embodiments, the disclosure provides a pharmaceutical composition comprising a RNAi oligonucleotide described herein, and a pharmaceutically acceptable carrier, delivery agent or excipient.

[0037] In other embodiments, the disclosure provides a method of delivering an oligonucleotide to a subject, the method comprising administering a pharmaceutical composition described herein to the subject.

[0038] In another embodiments, the disclosure provides a method for reducing *LPA* expression in a cell, a population of cells or a subject, the method comprising the step of:

- i. contacting the cell or the population of cells with a RNAi oligonucleotide or pharmaceutical composition described herein; or
- ii. administering to the subject a RNAi oligonucleotide or pharmaceutical composition described herein. In some embodiments, reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of *LPA* protein, or both. In some embodiments, the subject has a disease, disorder or condition associated with *LPA* expression. In some embodiments, the disease, disorder, or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH. In some embodiments, the RNAi

oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

[0039] In another aspect, the disclosure provides a method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

[0040] In another aspect, the disclosure provides a method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in **Table 5**, or pharmaceutical composition thereof, thereby treating the subject.

[0041] In other embodiments, the disclosure provides a method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 393 and 793, respectively;
- (b) SEQ ID NOs: 388 and 788, respectively;
- (c) SEQ ID NOs: 389 and 789, respectively;
- (d) SEQ ID NOs: 390 and 790, respectively;
- (e) SEQ ID NOs: 391 and 791, respectively;
- (f) SEQ ID NOs: 392 and 792, respectively;
- (g) SEQ ID NOs: 394 and 794, respectively;
- (h) SEQ ID NOs: 395 and 795, respectively;
- (i) SEQ ID NOs: 396 and 796, respectively;
- (j) SEQ ID NOs: 397 and 797, respectively;
- (k) SEQ ID NOs: 398 and 798, respectively;
- (l) SEQ ID NOs: 399 and 799, respectively;
- (m) SEQ ID NOs: 400 and 800, respectively;
- (n) SEQ ID NOs: 401 and 801, respectively;

- (o) SEQ ID NOs: 402 and 802, respectively; and
- (p) SEQ ID NOs: 403 and 803, respectively.

[0042] In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 393, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 793. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 388, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 788. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 389, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 789. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 390, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 790. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 391, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 791. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 392, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 394, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 794. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 395, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 795. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 396, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 796. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 397, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 797. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 398, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 798. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 399, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 799. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 400, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 800. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 401, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 801. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in

SEQ ID NO: 402, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 802. In some embodiments, the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 403, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 803.

[0043] In some embodiments, the disease, disorder, or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

[0044] In some embodiments, the disclosure provides use of an RNAi oligonucleotide or pharmaceutical composition described herein, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with *LPA* expression, optionally for the treatment of a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

[0045] In some embodiments, the disclosure provides use of an RNAi oligonucleotide or pharmaceutical composition described herein, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *LPA* expression, optionally for the treatment of a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

[0046] In other embodiments, the disclosure provides a kit comprising an RNAi oligonucleotide described herein, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with *LPA* expression.

[0047] In any of the foregoing or related embodiments, the disease, disorder, or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

BRIEF DESCRIPTION OF THE DRAWINGS

[0048] **FIGs. 1-4** provide graphs depicting the percent (%) of *LPA* mRNA in HEK293-*LPA* cells transfected with the indicated DsiRNAs relative to the % of *LPA* mRNA control mock-treated cells.

[0049] **FIG. 5** provides a graph depicting the percent (%) of *LPA* mRNA in HepG2-*LPA* cells transfected with the indicated DsiRNAs relative to the % of *LPA* mRNA control mock-treated cells.

[0050] **FIGs. 6-7** provide graphs depicting the percent (%) of *LPA* mRNA in HEK293-*LPA* cells transfected with the indicated DsiRNAs relative to the % of *LPA* mRNA control mock-treated cells.

[0051] **FIGs. 8-9** provide graphs depicting the percent (%) of LPA mRNA in liver samples from mice treated with the indicated GalNAc-conjugated LPA oligonucleotides relative to mice treated with phosphate buffered saline (PBS).

[0052] **FIG. 10** provides a schematic depicting the structure and chemical modification patterns of generic N-Acetylgalactosamine (GalNAc)-conjugated LPA oligonucleotides.

[0053] **FIGs. 11A-11C** provide graphs depicting the percent (%) of LPA mRNA in liver samples from non-human primates (NHPs) treated with the indicated GalNAc-conjugated LPA oligonucleotides relative to NHPs treated with PBS on day 28 (**FIG. 11A**), day 56 (**FIG. 11B**) and day 84 (**FIG. 11C**) following treatment.

[0054] **FIG. 11D** provides a graph depicting the percent (%) of PLG mRNA in liver samples from NHPs treated with the indicated GalNAc-conjugated LPA oligonucleotides relative to NHPs treated with PBS on day 28.

[0055] **FIG. 12** provides a graph depicting the mean percent (%) of apo(a) protein in serum from NHPs treated with the indicated GalNAc-conjugated LPA oligonucleotides relative to NHPs treated with PBS over time.

DETAILED DESCRIPTION

I. Definitions

[0056] As used herein, “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0057] As used herein, “administer,” “administering,” “administration” and the like refers to providing a substance (*e.g.*, an oligonucleotide) to a subject in a manner that is pharmacologically useful (*e.g.*, to treat a condition in the subject).

[0058] As used herein, the term “apolipoprotein(a)” and abbreviated as “apo(a)”, refers to the apolipoprotein(a) polypeptide, which is a member of the apolipoprotein class of polypeptides that bind lipids to form lipoproteins. Apo(a) is a polymorphic glycoprotein encoded by the *LPA* gene in humans. *LPA* mRNA and apo(a) polypeptide are expressed predominantly in the liver. Lipoprotein(a) (abbreviated as Lp(a)) is a class of lipoprotein formed in the liver and comprises a single copy of apolipoprotein (apo) B-100 (Apo-B100) covalently tethered to apo(a). In humans, apo(a) includes at least 10 subtypes of KIV repeats,

composed of 1 copy each of KIV₁, multiple copies of KIV₂, and 1 copy each of KIV₃-KIV₁₀, KV, and an inactive protease-like domain. The presence of apo(a) distinguishes Lp(a) from all other lipoprotein classes (Marcovina et al., (1995) Clin Chem. 41(2):246-55). For the purposes of the disclosure, “apolipoprotein(a)” or “apo(a)” refers to the apo(a) polypeptide from any vertebrate or mammal including, but not limited to, human, mouse, primate, monkey, bovine, chicken, rodent, rat, porcine, ovine and guinea pig. “Apo(a)” also refers to fragments and variants of native apo(a) that maintain at least one *in vivo* or *in vitro* activity of a native apo(a). Apo(a) encompasses full-length, unprocessed precursor forms of Apo(a), as well as mature forms resulting from post-translational processing. An exemplary sequence of a human *LPA* mRNA transcript is publicly available (GenBank Accession No. NM_005577.3) and disclosed herein (SEQ ID NO: 1). An exemplary sequence of cynomolgus monkey *LPA* mRNA is publicly available (GenBank Accession No. XM_015448517.1) and disclosed herein (SEQ ID NO: 2).

[0059] As used herein, “asialoglycoprotein receptor” or “ASGPR” refers to a bipartite C-type lectin formed by a major 48 kDa subunit (ASGPR-1) and minor 40 kDa subunit (ASGPR-2). ASGPR is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing of circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins).

[0060] As used herein, “attenuate,” “attenuating,” “attenuation” and the like refers to reducing or effectively halting. As a non-limiting example, one or more of the treatments herein may reduce or effectively halt the onset or progression of cardiometabolic diseases including atherosclerosis, dyslipidemia, NAFLD and NASH in a subject. This attenuation may be exemplified by, for example, a decrease in one or more aspects (*e.g.*, symptoms, tissue characteristics, and cellular, inflammatory or immunological activity, *etc.*) of cardiometabolic diseases including atherosclerosis, dyslipidemia, NAFLD and NASH, no detectable progression (worsening) of one or more aspects of cardiometabolic diseases including atherosclerosis, dyslipidemia, NAFLD and NASH, or no detectable aspects of cardiometabolic diseases including atherosclerosis, dyslipidemia, NAFLD and NASH in a subject when they might otherwise be expected.

[0061] As used herein, “complementary” refers to a structural relationship between two nucleotides (*e.g.*, on two opposing nucleic acids or on opposing regions of a single nucleic acid strand) that permits the two nucleotides to form base pairs with one another. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. In

some embodiments, complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. In some embodiments, two nucleic acids may have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

[0062] As used herein, “deoxyribonucleotide” refers to a nucleotide having a hydrogen in place of a hydroxyl at the 2' position of its pentose sugar when compared with a ribonucleotide. A modified deoxyribonucleotide is a deoxyribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the sugar, phosphate group or base.

[0063] As used herein, “double-stranded oligonucleotide” or “ds oligonucleotide” refers to an oligonucleotide that is substantially in a duplex form. In some embodiments, the complementary base-pairing of duplex region(s) of a ds oligonucleotide is formed between antiparallel sequences of nucleotides of covalently separate nucleic acid strands. In some embodiments, complementary base-pairing of duplex region(s) of a ds oligonucleotide is formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. In some embodiments, complementary base-pairing of duplex region(s) of a ds oligonucleotide is formed from single nucleic acid strand that is folded (*e.g.*, *via* a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. In some embodiments, a ds oligonucleotide comprises two covalently separate nucleic acid strands that are fully duplexed with one another. However, in some embodiments, a ds oligonucleotide comprises two covalently separate nucleic acid strands that are partially duplexed (*e.g.*, having overhangs at one or both ends). In some embodiments, a ds oligonucleotide comprises antiparallel sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

[0064] As used herein, “duplex,” in reference to nucleic acids (*e.g.*, oligonucleotides), refers to a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

[0065] As used herein, “excipient” refers to a non-therapeutic agent that may be included in a composition, for example, to provide or contribute to a desired consistency or stabilizing effect.

[0066] As used herein, “hepatocyte” or “hepatocytes” refers to cells of the parenchymal tissues of the liver. These cells make up about 70%-85% of the liver's mass and manufacture serum albumin, FBN and the prothrombin group of clotting factors (except for Factors 3 and 4). Markers for hepatocyte lineage cells include, but are not limited to, transthyretin (Ttr),

glutamine synthetase (Glut), hepatocyte nuclear factor 1a (Hnf1a) and hepatocyte nuclear factor 4a (Hnf4a). Markers for mature hepatocytes may include, but are not limited to, cytochrome P450 (Cyp3a11), fumarylacetoacetate hydrolase (Fah), glucose 6-phosphate (G6p), albumin (Alb) and OC2-2F8. *See, e.g., Huch et al. (2013) Nature 494:247-250.*

[0067] As used herein, a “hepatotoxic agent” refers to a chemical compound, virus or other substance that is itself toxic to the liver or can be processed to form a metabolite that is toxic to the liver. Hepatotoxic agents may include, but are not limited to, carbon tetrachloride (CCl₄), acetaminophen (paracetamol), vinyl chloride, arsenic, chloroform, nonsteroidal anti-inflammatory drugs (such as aspirin and phenylbutazone).

[0068] As used herein, “labile linker” refers to a linker that can be cleaved (*e.g.*, by acidic pH). A “fairly stable linker” refers to a linker that cannot be cleaved.

[0069] As used herein, “liver inflammation” or “hepatitis” refers to a physical condition in which the liver becomes swollen, dysfunctional and/or painful, especially as a result of injury or infection, as may be caused by exposure to a hepatotoxic agent. Symptoms may include jaundice (yellowing of the skin or eyes), fatigue, weakness, nausea, vomiting, appetite reduction and weight loss. Liver inflammation, if left untreated, may progress to fibrosis, cirrhosis, liver failure or liver cancer.

[0070] As used herein, “liver fibrosis” or “fibrosis of the liver” refers to an excessive accumulation in the liver of extracellular matrix proteins, which could include collagens (I, III, and IV), FBN, undulin, elastin, laminin, hyaluronan and proteoglycans resulting from inflammation and liver cell death. Liver fibrosis, if left untreated, may progress to cirrhosis, liver failure or liver cancer.

[0071] As used herein, “loop” refers to a unpaired region of a nucleic acid (*e.g.*, oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cells), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a “stem”).

[0072] As used herein, “modified internucleotide linkage” refers to an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage comprising a phosphodiester bond. In some embodiments, a modified nucleotide is a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a modified nucleotide may improve thermal stability,

resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

[0073] As used herein, “modified nucleotide” refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide and thymidine deoxyribonucleotide. In some embodiments, a modified nucleotide is a non-naturally occurring nucleotide. In some embodiments, a modified nucleotide has one or more chemical modification in its sugar, nucleobase and/or phosphate group. In some embodiments, a modified nucleotide has one or more chemical moieties conjugated to a corresponding reference nucleotide. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

[0074] As used herein, “nicked tetraloop structure” refers to a structure of a RNAi oligonucleotide that is characterized by separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

[0075] As used herein, “oligonucleotide” refers to a short nucleic acid (*e.g.*, less than about 100 nucleotides in length). An oligonucleotide may be single-stranded (ss) or ds. An oligonucleotide may or may not have duplex regions. As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (dsiRNA), antisense oligonucleotide, short siRNA or ss siRNA. In some embodiments, a ds oligonucleotide is an RNAi oligonucleotide.

[0076] As used herein, “overhang” refers to terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which the one strand or region forms a duplex. In some embodiments, an overhang comprises one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a ds oligonucleotide. In certain embodiments, the overhang is a 3' or 5' overhang on the antisense strand or sense strand of a ds oligonucleotides.

[0077] As used herein, “phosphate analog” refers to a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate

analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. In some embodiments, a 5' phosphate analog contains a phosphatase-resistant linkage. Examples of phosphate analogs include, but are not limited to, 5' phosphonates, such as 5' methylenephosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog") at a 5'-terminal nucleotide. An example of a 4'-phosphate analog is oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. *See, e.g.*, US Provisional Patent Application Nos. 62/383,207 (filed on 2 September 2016) and 62/393,401 (filed on 12 September 2016). Other modifications have been developed for the 5' end of oligonucleotides (*see, e.g.*, Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash *et al.* (2015) *Nucleic Acids Res.* 43:2993-3011).

[0078] As used herein, "reduced expression" of a gene (*e.g.*, *LPA*) refers to a decrease in the amount or level of RNA transcript (*e.g.*, *LPA* mRNA) or protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a sample or a subject, when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample or subject). For example, the act of contacting a cell with an oligonucleotide herein (*e.g.*, an oligonucleotide comprising an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence comprising *LPA* mRNA) may result in a decrease in the amount or level of *LPA* mRNA, apo(a) protein and/or apo(a) activity (*e.g.*, *via* inactivation and/or degradation of *LPA* mRNA by the RNAi pathway) when compared to a cell that is not treated with the ds oligonucleotide. Similarly, and as used herein, "reducing expression" refers to an act that results in reduced expression of a gene (*e.g.*, *LPA*). As used herein, "reduction of *LPA* expression" refers to a decrease in the amount or level of *LPA* mRNA, apo(a) protein and/or apo(a) activity in a cell, a population of cells, a sample or a subject when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample, or subject).

[0079] As used herein, "region of complementarity" refers to a sequence of nucleotides of a nucleic acid (*e.g.*, a ds oligonucleotide) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cell, *etc.*). In some embodiments, an oligonucleotide herein comprises a targeting sequence having a region of complementarity to a mRNA target sequence.

[0080] As used herein, “ribonucleotide” refers to a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2' position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the ribose, phosphate group or base.

[0081] As used herein, “RNAi oligonucleotide” refers to either (a) a ds oligonucleotide having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the Argonaute 2 (Ago2) endonuclease in the cleavage of a target mRNA (*e.g.*, *LPA* mRNA) or (b) a ss oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA (*e.g.*, *LPA* mRNA).

[0082] As used herein, “strand” refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (*e.g.*, phosphodiester linkages or phosphorothioate linkages). In some embodiments, a strand has two free ends (*e.g.*, a 5' end and a 3' end).

[0083] As used herein, “subject” means any mammal, including mice, rabbits and humans. In one embodiment, the subject is a human or NHP. Moreover, “individual” or “patient” may be used interchangeably with “subject.”

[0084] As used herein, “synthetic” refers to a nucleic acid or other molecule that is artificially synthesized (*e.g.*, using a machine (*e.g.*, a solid-state nucleic acid synthesizer)) or that is otherwise not derived from a natural source (*e.g.*, a cell or organism) that normally produces the molecule.

[0085] As used herein, “targeting ligand” refers to a molecule (*e.g.*, a carbohydrate, amino sugar, cholesterol, polypeptide or lipid) that selectively binds to a cognate molecule (*e.g.*, a receptor) of a tissue or cell of interest and that is conjugatable to another substance for purposes of targeting the other substance to the tissue or cell of interest. For example, in some embodiments, a targeting ligand may be conjugated to an oligonucleotide for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. In some embodiments, a targeting ligand selectively binds to a cell surface receptor. Accordingly, in some embodiments, a targeting ligand when conjugated to an oligonucleotide facilitates delivery of the oligonucleotide into a particular cell through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand and receptor. In some embodiments, a targeting ligand is conjugated to an oligonucleotide *via* a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell.

[0086] As used herein, “tetraloop” refers to a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a tetraloop can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C or at least about 75°C in 10 mM NaHPO₄ to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. In some embodiments, a tetraloop may stabilize a bp in an adjacent stem duplex by stacking interactions. In addition, interactions among the nucleotides in a tetraloop include, but are not limited to, non-Watson-Crick base pairing, stacking interactions, hydrogen bonding and contact interactions (Cheong *et al.* (1990) *NATURE* 346:680-82; Heus & Pardi (1991) *SCIENCE* 253:191-94). In some embodiments, a tetraloop comprises or consists of 3 to 6 nucleotides and is typically 4 to 5 nucleotides. In certain embodiments, a tetraloop comprises or consists of 3, 4, 5 or 6 nucleotides, which may or may not be modified (*e.g.*, which may or may not be conjugated to a targeting moiety). In one embodiment, a tetraloop consists of 4 nucleotides. Any nucleotide may be used in the tetraloop and standard IUPAC-IUB symbols for such nucleotides may be used as described in Cornish-Bowden (1985) *Nucleic Acids Res.* 13:3021-3030. For example, the letter “N” may be used to mean that any base may be in that position, the letter “R” may be used to show that A (adenine) or G (guanine) may be in that position, and “B” may be used to show that C (cytosine), G (guanine), T (thymine) or U (uracil) may be in that position. Examples of tetraloops include the UNCG family of tetraloops (*e.g.*, UUCG), the GNRA family of tetraloops (*e.g.*, GAAA), and the CUUG tetraloop (Woese *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:8467-8471; Antao *et al.* (1991) *Nucleic Acids Res.* 19:5901-5905). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (*e.g.*, d(GTTA), the d(GNRA)) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (*e.g.*, d(TTCG)). *See, e.g.*, Nakano *et al.* (2002) *Biochem.* 41:4281-14292; Shinji *et al.* (2000) *Nippon Kagakkai Koen Yokoshu* 78:731. In some embodiments, the tetraloop is contained within a nicked tetraloop structure.

[0087] As used herein, “treat” or “treating” refers to the act of providing care to a subject in need thereof, for example, by administering a therapeutic agent (*e.g.*, an oligonucleotide herein) to the subject, for purposes of improving the health and/or well-being of the subject with respect to an existing condition (*e.g.*, a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. In some embodiments, treatment involves reducing the frequency

or severity of at least one sign, symptom or contributing factor of a condition (*e.g.*, disease, disorder) experienced by a subject.

II. Oligonucleotide Inhibitors of *LPA* Expression

[0088] The disclosure provides, *inter alia*, oligonucleotides that inhibit *LPA* expression. In some embodiments, an oligonucleotide that inhibits *LPA* expression herein is targeted to an *LPA* mRNA.

i. *LPA* Target Sequences

[0089] In some embodiments, the oligonucleotide is targeted to a target sequence comprising an *LPA* mRNA. In some embodiments, the oligonucleotide, or a portion, fragment or strand thereof (*e.g.*, an antisense strand or a guide strand of a ds oligonucleotide) binds or anneals to a target sequence comprising an *LPA* mRNA, thereby inhibiting *LPA* expression. In some embodiments, the oligonucleotide is targeted to an *LPA* target sequence for the purpose of inhibiting *LPA* expression *in vivo*. In some embodiments, the amount or extent of inhibition of *LPA* expression by an oligonucleotide targeted to an *LPA* target sequence correlates with the potency of the oligonucleotide. In some embodiments, the amount or extent of inhibition of *LPA* expression by an oligonucleotide targeted to an *LPA* target sequence correlates with the amount or extent of therapeutic benefit in a subject or patient having a disease, disorder or condition associated with the expression of *LPA* treated with the oligonucleotide.

[0090] Through examination and analysis of the nucleotide sequence of *LPA* mRNAs encoding apo(a), including mRNAs of multiple different species (*e.g.*, human, cynomolgus monkey, and rhesus monkey; *see, e.g.*, **Example 1**) and as a result of *in vitro* and *in vivo* testing (*see, e.g.*, **Example 2** and **Example 3**), it has been discovered that certain nucleotide sequences of *LPA* mRNA are more amenable than others to oligonucleotide-based inhibition of *LPA* expression and are thus useful as target sequences for the oligonucleotides herein. In some embodiments, a sense strand of an oligonucleotide (*e.g.*, a ds oligonucleotide) described herein (*e.g.*, in **Table 5**) comprises an *LPA* target sequence. In some embodiments, a portion or region of the sense strand of a ds oligonucleotide described herein (*e.g.*, in **Table 5**) comprises an *LPA* target sequence. In some embodiments, an *LPA* target sequence comprises, or consists of, a sequence of any one of SEQ ID Nos: 4-387.

ii. *LPA* Targeting Sequences

[0091] In some embodiments, the oligonucleotides herein have regions of complementarity to *LPA* mRNA (*e.g.*, within a target sequence of *LPA* mRNA) for purposes of targeting the *LPA* mRNA in cells and inhibiting *LPA* expression. In some embodiments, the oligonucleotides

herein comprise an *LPA* targeting sequence (*e.g.*, an antisense strand or a guide strand of a ds oligonucleotide) having a region of complementarity that binds or anneals to an *LPA* target sequence by complementary (Watson-Crick) base pairing. The targeting sequence or region of complementarity is generally of a suitable length and base content to enable binding or annealing of the oligonucleotide (or a strand thereof) to an *LPA* mRNA for purposes of inhibiting its expression. In some embodiments, the targeting sequence or region of complementarity is at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29 or at least about 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12 to about 30 (*e.g.*, 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 24 nucleotides in length.

[0092] In some embodiments, an oligonucleotide herein comprises a targeting sequence or a region of complementarity (*e.g.*, an antisense strand or a guide strand of a double-stranded oligonucleotide) that is fully complementary to an *LPA* target sequence. In some embodiments, the targeting sequence or region of complementarity is partially complementary to an *LPA* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 4-387. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 4-387.

[0093] In some embodiments, the oligonucleotide herein comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides

comprising an *LPA* mRNA, wherein the contiguous sequence of nucleotides is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 28, 12 to 26, 12 to 24, 12 to 20, 12 to 18, 12 to 16, 14 to 22, 16 to 20, 18 to 20 or 18 to 19 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an *LPA* mRNA, wherein the contiguous sequence of nucleotides is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an *LPA* mRNA, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an *LPA* mRNA, wherein the contiguous sequence of nucleotides is 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 4-387, optionally wherein the contiguous sequence of nucleotides is 19 nucleotides in length.

[0094] In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 4-387 and spans the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 4-387 and spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein comprises a region of complementarity (*e.g.*, on an antisense strand of a ds oligonucleotide) that is at least partially (*e.g.*, fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20 of a sequence as set forth in any one of SEQ ID NOs: 4-387.

[0095] In some embodiments, an oligonucleotide herein comprises a targeting sequence or region of complementarity having one or more base pair (bp) mismatches with the corresponding *LPA* target sequence. In some embodiments, the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *LPA* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *LPA* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to reduce or inhibit *LPA* expression is maintained. Alternatively, in some embodiments, the targeting

sequence or region of complementarity comprises no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *LPA* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *LPA* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to reduce or inhibit *LPA* expression is maintained. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 1 mismatch with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 2 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 3 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 4 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 5 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, wherein at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or wherein the mismatches are interspersed in any position throughout the targeting sequence or region of complementarity. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, wherein at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or wherein at least one or more non-mismatched base pair is located between the mismatches, or a combination thereof.

iii. Types of Oligonucleotides

[0096] A variety of oligonucleotide types and/or structures are useful for targeting *LPA* mRNA in the methods herein including, but not limited to, RNAi oligonucleotides, antisense oligonucleotides, miRNAs, *etc.* Any of the oligonucleotide types described herein or elsewhere are contemplated for use as a framework to incorporate an *LPA* mRNA targeting sequence herein for the purposes of inhibiting *LPA* expression.

[0097] In some embodiments, the oligonucleotides herein inhibit *LPA* expression by engaging with RNA interference (RNAi) pathways upstream or downstream of Dicer involvement. For example, RNAi oligonucleotides have been developed with each strand having sizes of about 19-25 nucleotides with at least one 3' overhang of 1 to 5 nucleotides (*see*,

e.g., US Patent No. 8,372,968). Longer oligonucleotides also have been developed that are processed by Dicer to generate active RNAi products (*see, e.g.*, US Patent No. 8,883,996). Further work produced extended ds oligonucleotides where at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically-stabilizing tetraloop structure (*see, e.g.*, US Patent Nos. 8,513,207 and 8,927,705, as well as Intl. Patent Application Publication No. WO 2010/033225). Such structures may include ss extensions (on one or both sides of the molecule) as well as ds extensions.

[0098] In some embodiments, the oligonucleotides herein engage with the RNAi pathway downstream of the involvement of Dicer (*e.g.*, Dicer cleavage). In some embodiments, the oligonucleotide has an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3' end of the sense strand. In some embodiments, the oligonucleotide (*e.g.*, siRNA) comprises a 21-nucleotide guide strand that is antisense to a target mRNA (*e.g.*, *LPA* mRNA) and a complementary passenger strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3' ends. Longer oligonucleotide designs also are contemplated including oligonucleotides having a guide strand of 23 nucleotides and a passenger strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a two nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 21 bp duplex region. *See, e.g.*, US Patent Nos. 9,012,138; 9,012,621 and 9,193,753.

[0099] In some embodiments, the oligonucleotides herein comprise sense and antisense strands that are both in the range of about 17 to 26 (*e.g.*, 17 to 26, 20 to 25 or 21-23) nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense and antisense strand that are both in the range of about 19-22 nucleotides in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, an oligonucleotide comprises sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, for oligonucleotides that have sense and antisense strands that are both in the range of about 21-23 nucleotides in length, a 3' overhang on the sense, antisense, or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotide has a guide strand of 22 nucleotides and a passenger strand of 20 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a 2

nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 20 bp duplex region.

[0100] Other oligonucleotide designs for use with the compositions and methods herein include: 16-mer siRNAs (*see, e.g.*, NUCLEIC ACIDS IN CHEMISTRY AND BIOLOGY, Blackburn (ed.), Royal Society of Chemistry, 2006), shRNAs (*e.g.*, having 19 bp or shorter stems; *see, e.g.*, Moore *et al.* (2010) METHODS MOL. BIOL. 629:141-58), blunt siRNAs (*e.g.*, of 19 bps in length; *see, e.g.*, Kraynack & Baker (2006) RNA 12:163-76), asymmetrical siRNAs (aiRNA; *see, e.g.*, Sun *et al.* (2008) NAT. BIOTECHNOL. 26:1379-82), asymmetric shorter-duplex siRNA (*see, e.g.*, Chang *et al.* (2009) MOL. THER. 17:725-32), fork siRNAs (*see, e.g.*, Hohjoh (2004) FEBS LETT. 557:193-198), ss siRNAs (Elsner (2012) NAT. BIOTECHNOL. 30:1063), dumbbell-shaped circular siRNAs (*see, e.g.*, Abe *et al.* (2007) J. AM. CHEM. SOC. 129:15108-09), and small internally segmented interfering RNA (siRNA; *see, e.g.*, Bramsen *et al.* (2007) NUCLEIC ACIDS RES. 35:5886-97). Further non-limiting examples of an oligonucleotide structures that may be used in some embodiments to reduce or inhibit the expression of *LPA* are microRNA (miRNA), short hairpin RNA (shRNA) and short siRNA (*see, e.g.*, Hamilton *et al.* (2002) EMBO J. 21:4671-79; *see also*, US Patent Application Publication No. 2009/0099115).

[0101] Still, in some embodiments, an oligonucleotide for reducing or inhibiting *LPA* expression herein is single-stranded (ss). Such structures may include but are not limited to ss RNAi molecules. Recent efforts have demonstrated the activity of ss RNAi molecules (*see, e.g.*, Matsui *et al.* (2016) Mol. Ther. 24:946-955). However, in some embodiments, oligonucleotides herein are antisense oligonucleotides (ASOs). An antisense oligonucleotide is a ss oligonucleotide that has a nucleobase sequence which, when written or depicted in the 5' to 3' direction, comprises the reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (*e.g.*, as a gapmer) so as to induce RNaseH-mediated cleavage of its target RNA in cells or (*e.g.*, as a mixmer) so as to inhibit translation of the target mRNA in cells. ASOs for use herein may be modified in any suitable manner known in the art including, for example, as shown in US Patent No. 9,567,587 (including, *e.g.*, length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, ASOs have been used for decades to reduce expression of specific target genes (*see, e.g.*, Bennett *et al.* (2017) Annu. Rev. Pharmacol. 57:81-105).

iv. Double-Stranded Oligonucleotides

[0102] The disclosure provides double-stranded (ds) oligonucleotides for targeting *LPA* mRNA and inhibiting *LPA* expression (*e.g.*, via the RNAi pathway) comprising a sense strand

(also referred to herein as a passenger strand) and an antisense strand (also referred to herein as a guide strand). In some embodiments, the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked.

[0103] In some embodiments, the sense strand has a first region (R1) and a second region (R2), wherein R2 comprises a first subregion (S1), a tetraloop (L) or triloop (triL), and a second subregion (S2), wherein L or triL is located between S1 and S2, and wherein S1 and S2 form a second duplex (D2). D2 may have various lengths. In some embodiments, D2 is about 1-6 bp in length. In some embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5 or 4-5 bp in length. In some embodiments, D2 is 1, 2, 3, 4, 5 or 6 bp in length. In some embodiments, D2 is 6 bp in length.

[0104] In some embodiments, R1 of the sense strand and the antisense strand form a first duplex (D1). In some embodiments, D1 is at least about 15 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21) nucleotides in length. In some embodiments, D1 is in the range of about 12 to 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30 or 21 to 30 nucleotides in length). In some embodiments, D1 is at least 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 20, at least 25, or at least 30 nucleotides in length). In some embodiments, D1 is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, D1 is 20 nucleotides in length. In some embodiments, D1 comprising sense strand and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, D1 comprising the sense strand and antisense strand spans the entire length of either the sense strand or antisense strand or both. In certain embodiments, D1 comprising the sense strand and antisense strand spans the entire length of both the sense strand and the antisense strand.

[0105] In some embodiments, a ds oligonucleotide herein comprises a sense strand having a sequence of any one of SEQ ID NOs: 388-403 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 788-803, as is arranged **Table 3**. In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 393 and the antisense strand comprises the sequence of SEQ ID NO: 793.

[0106] It should be appreciated that, in some embodiments, sequences presented in the Sequence Listing may be referred to in describing the structure of an oligonucleotide (*e.g.*, a ds oligonucleotide) or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides (*e.g.*, an RNA counterpart of

a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[0107] In some embodiments, a ds oligonucleotide herein comprises a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In some embodiments, the sense strand of the ds oligonucleotide is longer than 27 nucleotides (*e.g.*, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides). In some embodiments, the sense strand of the ds oligonucleotide is longer than 25 nucleotides (*e.g.*, 26, 27, 28, 29 or 30 nucleotides).

[0108] In some embodiments, the ds oligonucleotides herein have one 5' end that is thermodynamically less stable when compared to the other 5' end. In some embodiments, an asymmetric ds oligonucleotide is provided that comprises a blunt end at the 3' end of a sense strand and a 3'-overhang at the 3' end of an antisense strand. In some embodiments, the 3'-overhang on the antisense strand is about 1-8 nucleotides in length (*e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). Typically, a ds oligonucleotide for RNAi has a two-nucleotide overhang on the 3' end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3'-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides. However, in some embodiments, the overhang is a 5'-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides.

[0109] In some embodiments, two terminal nucleotides on the 3' end of an antisense strand are modified. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are complementary with the target mRNA (*e.g.*, *LPA* mRNA). In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are not complementary with the target mRNA. In some embodiments, two terminal nucleotides on each 3' end of an oligonucleotide in the nicked tetraloop structure are GG. Typically, one or both of the two terminal GG nucleotides on each 3' end of a ds oligonucleotide is not complementary with the target mRNA.

[0110] In some embodiments, there is one or more (*e.g.*, 1, 2, 3, 4 or 5) mismatch(s) between a sense and antisense strand. If there is more than one mismatch between a sense and antisense strand, they may be positioned consecutively (*e.g.*, 2, 3 or more in a row), or interspersed

throughout the region of complementarity. In some embodiments, the 3' end of the sense strand contains one or more mismatches. In one embodiment, two mismatches are incorporated at the 3' end of the sense strand. In some embodiments, base mismatches, or destabilization of segments at the 3' end of the sense strand of the oligonucleotide improves or increases the potency of the ds oligonucleotide.

a. Antisense Strands

[0111] In some embodiments, an oligonucleotide (*e.g.*, a ds oligonucleotide) disclosed herein for targeting *LPA* mRNA and inhibiting *LPA* expression comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 404-803. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising or consisting of at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 404-803.

[0112] In some embodiments, an oligonucleotide (*e.g.*, a ds oligonucleotide) herein comprises an antisense strand of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, an oligonucleotide may have an antisense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 22, at least 25, at least 27, at least 30, at least 35 or at least 38 nucleotides in length). In some embodiments, an oligonucleotide may have an antisense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 22, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40 or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide may have an antisense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides in length.

[0113] In some embodiments, an antisense strand of an oligonucleotide is referred to as a "guide strand." For example, an antisense strand that engages with RNA-induced silencing complex (RISC) and binds to an Argonaute protein such as Ago2, or engages with or binds to one or more similar factors, and directs silencing of a target gene, the antisense strand is referred to as a guide strand. In some embodiments, a sense strand complementary to a guide strand is referred to as a "passenger strand."

b. Sense Strands

[0114] In some embodiments, an oligonucleotide (*e.g.*, a ds oligonucleotide) herein for targeting *LPA* mRNA and inhibiting *LPA* expression comprises or consists of a sense strand

sequence as set forth in in any one of SEQ ID NOs: 4-403. In some embodiments, an oligonucleotide has a sense strand that comprises or consists of at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in in any one of SEQ ID NOs: 4-403.

[0115] In some embodiments, an oligonucleotide (*e.g.*, a ds oligonucleotide) herein comprises a sense strand (or passenger strand) of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 36, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, an oligonucleotide may have a sense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 36 or at least 38 nucleotides in length). In some embodiments, an oligonucleotide may have a sense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40 or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide may have a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides in length.

[0116] In some embodiments, a sense strand comprises a stem-loop structure at its 3' end. In some embodiments, a sense strand comprises a stem-loop structure at its 5' end. In some embodiments, a stem is a duplex of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 bp in length. In some embodiments, a stem-loop provides the oligonucleotide protection against degradation (*e.g.*, enzymatic degradation) and facilitates or improves targeting and/or delivery to a target cell, tissue, or organ (*e.g.*, the liver), or both. For example, in some embodiments, the loop of a stem-loop provides nucleotides comprising one or more modifications that facilitate, improve, or increase targeting to a target mRNA (*e.g.*, an *LPA* mRNA), inhibition of target gene expression (*e.g.*, *LPA* expression), and/or delivery to a target cell, tissue, or organ (*e.g.*, the liver), or both. In some embodiments, the stem-loop itself or modification(s) to the stem-loop do not substantially affect the inherent gene expression inhibition activity of the oligonucleotide, but facilitates, improves, or increases stability (*e.g.*, provides protection against degradation) and/or delivery of the oligonucleotide to a target cell, tissue, or organ (*e.g.*, the liver). In certain embodiments, an oligonucleotide comprises a sense strand comprising (*e.g.*, at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). In some embodiments, the loop (L) is 4 nucleotides in length. **FIG. 10** depicts a non-limiting example of such an oligonucleotide.

In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described above is a tetraloop (*e.g.*, within a nicked tetraloop structure). In some embodiments, the tetraloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, delivery ligands, and combinations thereof.

v. Oligonucleotide Modifications

a. Sugar Modifications

[0117] In some embodiments, a modified sugar (also referred herein to a sugar analog) includes a modified deoxyribose or ribose moiety in which, for example, one or more modifications occur at the 2', 3', 4' and/or 5' carbon position of the sugar. In some embodiments, a modified sugar may also include non-natural alternative carbon structures such as those present in locked nucleic acids ("LNA"; *see, e.g.*, Koshkin *et al.* (1998) TETRAHEDON 54:3607-30), unlocked nucleic acids ("UNA"; *see, e.g.*, Snead *et al.* (2013) MOL. THER-NUCL. ACIDS 2:e103) and bridged nucleic acids ("BNA"; *see, e.g.*, Imanishi & Obika (2002) CHEM COMMUN. (CAMB) 21:1653-59).

[0118] In some embodiments, a nucleotide modification in a sugar comprises a 2'-modification. In some embodiments, a 2'-modification may be 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-fluoro (2'-F), 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA) or 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA). In some embodiments, the modification is 2'-F, 2'-OMe or 2'-MOE. In some embodiments, a modification in a sugar comprises a modification of the sugar ring, which may comprise modification of one or more carbons of the sugar ring. For example, a modification of a sugar of a nucleotide may comprise a 2'-oxygen of a sugar is linked to a 1'-carbon or 4'-carbon of the sugar, or a 2'-oxygen is linked to the 1'-carbon or 4'-carbon *via* an ethylene or methylene bridge. In some embodiments, a modified nucleotide has an acyclic sugar that lacks a 2'-carbon to 3'-carbon bond. In some embodiments, a modified nucleotide has a thiol group, *e.g.*, in the 4' position of the sugar.

[0119] In some embodiments, the oligonucleotide described herein comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand of the oligonucleotide comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand of the oligonucleotide comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, or more).

[0120] In some embodiments, all the nucleotides of the sense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the antisense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the oligonucleotide (*i.e.*, both the sense strand and the antisense strand) are modified. In some embodiments, the modified nucleotide comprises a 2'-modification (*e.g.*, a 2'-F or 2'-OMe, 2'-MOE, and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid). In some embodiments, the modified nucleotide comprises a 2'-modification (*e.g.*, a 2'-F or 2'-OMe)

[0121] The disclosure provides oligonucleotides having different modification patterns. In some embodiments, the modified oligonucleotides comprise a sense strand sequence having a modification pattern as set forth in any one of **Tables 3** and **4** (as well as **FIG. 10**) and an antisense strand having a modification pattern as set forth in any one of **Tables 3** and **4** (as well as **FIG. 10**). In some embodiments, for these oligonucleotides, one or more of positions 8, 9, 10 or 11 of the sense strand is modified with a 2'-F group. In other embodiments, for these oligonucleotides, the sugar moiety at each of nucleotides at positions 1-7 and 12-20 in the sense strand is modified with a 2'-OMe.

[0122] In some embodiments, the antisense strand has 3 nucleotides that are modified at the 2'-position of the sugar moiety with a 2'-F. In some embodiments, the sugar moiety at positions 2, 5 and 14 and optionally up to 3 of the nucleotides at positions 1, 3, 7 and 10 of the antisense strand are modified with a 2'-F. In other embodiments, the sugar moiety at each of the positions at positions 2, 5 and 14 of the antisense strand is modified with the 2'-F. In other embodiments, the sugar moiety at each of the positions at positions 1, 2, 5 and 14 of the antisense strand is modified with the 2'-F. In still other embodiments, the sugar moiety at each of the positions at positions 1, 2, 3, 5, 7 and 14 of the antisense strand is modified with the 2'-F. In yet another embodiment, the sugar moiety at each of the positions at positions 1, 2, 3, 5, 10 and 14 of the antisense strand is modified with the 2'-F. In another embodiment, the sugar moiety at each of the positions at positions 2, 3, 5, 7, 10 and 14 of the antisense strand is modified with the 2'-F.

b. 5' Terminal Phosphates

[0123] In some embodiments, 5'-terminal phosphate groups of an RNAi oligonucleotide enhance the interaction with Ago2. However, oligonucleotides comprising a 5'-phosphate group may be susceptible to degradation *via* phosphatases or other enzymes, which can limit their bioavailability *in vivo*. In some embodiments, an oligonucleotide (*e.g.*, a ds oligonucleotide) herein includes analogs of 5' phosphates that are resistant to such degradation. In some embodiments, the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonyl phosphonate, or a combination thereof. In certain embodiments, the 3' end of an

oligonucleotide strand is attached to chemical moiety that mimics the electrostatic and steric properties of a natural 5'-phosphate group ("phosphate mimic").

[0124] In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog"). *See, e.g.*, Intl. Patent Application Publication No. WO 2018/045317. In some embodiments, an oligonucleotide herein comprises a 4'-phosphate analog at a 5'-terminal nucleotide. In some embodiments, a phosphate analog is an oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. In other embodiments, a 4'-phosphate analog is a thiomethylphosphonate or an aminomethylphosphonate, in which the sulfur atom of the thiomethyl group or the nitrogen atom of the amino methyl group is bound to the 4'-carbon of the sugar moiety or analog thereof. In certain embodiments, a 4'-phosphate analog is an oxymethylphosphonate. In some embodiments, an oxymethylphosphonate is represented by the formula $-O-CH_2-PO(OH)_2$ or $-O-CH_2-PO(OR)_2$, in which R is independently selected from H, CH₃, an alkyl group, CH₂CH₂CN, CH₂OCOC(CH₃)₃, CH₂OCH₂CH₂Si(CH₃)₃ or a protecting group. In certain embodiments, the alkyl group is CH₂CH₃. More typically, R is independently selected from H, CH₃ or CH₂CH₃.

c. Modified Intranucleoside Linkages

[0125] In some embodiments, an oligonucleotide comprises a modified internucleoside linkage. In some embodiments, phosphate modifications or substitutions result in an oligonucleotide that comprises at least about 1 (*e.g.*, at least 1, at least 2, at least 3 or at least 5) modified internucleotide linkage. In some embodiments, any one of the oligonucleotides disclosed herein comprises about 1 to about 10 (*e.g.*, 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3 or 1 to 2) modified internucleotide linkages. In some embodiments, any one of the oligonucleotides disclosed herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 modified internucleotide linkages.

[0126] A modified internucleotide linkage may be a phosphorodithioate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage.

[0127] In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

strand. In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

d. Base Modifications

[0128] In some embodiments, oligonucleotides herein have one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1' position of a nucleotide sugar moiety. In certain embodiments, a modified nucleobase is a nitrogenous base. In certain embodiments, a modified nucleobase does not contain nitrogen atom. *See, e.g.*, US Patent Application Publication No. 2008/0274462. In some embodiments, a modified nucleotide comprises a universal base. However, in certain embodiments, a modified nucleotide does not contain a nucleobase (abasic).

[0129] In some embodiments, a universal base is a heterocyclic moiety located at the 1' position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a nucleotide sugar moiety substitution, that, when present in a duplex, can be positioned opposite more than one type of base without substantially altering structure of the duplex. In some embodiments, compared to a reference single-stranded nucleic acid (*e.g.*, oligonucleotide) that is fully complementary to a target nucleic acid, a single-stranded nucleic acid containing a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. However, in some embodiments, when compared to a reference single-stranded nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the single-stranded nucleic acid containing the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid comprising the mismatched base.

[0130] Non-limiting examples of universal-binding nucleotides include, but are not limited to, inosine, 1- β -D-ribofuranosyl-5-nitroindole and/or 1- β -D-ribofuranosyl-3-nitropyrrole (*see*, US Patent Application Publication No. 2007/0254362; Van Aerschot *et al.* (1995) NUCLEIC ACIDS RES. 23:4363-70; Loakes *et al.* (1995) NUCLEIC ACIDS RES. 23:2361-66; and Loakes & Brown (1994) NUCLEIC ACIDS RES. 22:4039-43).

e. Reversible Modifications

[0131] While certain modifications to protect an oligonucleotide from the *in vivo* environment before reaching target cells can be made, they can reduce the potency or activity of the oligonucleotide once it reaches the cytosol of the target cell. Reversible modifications

can be made such that the molecule retains desirable properties outside of the cell, which are then removed upon entering the cytosolic environment of the cell. Reversible modification can be removed, for example, by the action of an intracellular enzyme or by the chemical conditions inside of a cell (*e.g.*, through reduction by intracellular glutathione).

[0132] In some embodiments, a reversibly modified nucleotide comprises a glutathione-sensitive moiety. Typically, nucleic acid molecules have been chemically modified with cyclic disulfide moieties to mask the negative charge created by the internucleotide diphosphate linkages and improve cellular uptake and nuclease resistance. *See* US Patent Application Publication No. 2011/0294869, Intl. Patent Application Publication Nos. WO 2014/088920 and WO 2015/188197, and Meade *et al.* (2014) NAT. BIOTECHNOL. 32:1256-63. This reversible modification of the internucleotide diphosphate linkages is designed to be cleaved intracellularly by the reducing environment of the cytosol (*e.g.* glutathione). Earlier examples include neutralizing phosphotriester modifications that were reported to be cleavable inside cells (*see*, Dellinger *et al.* (2003) J. AM. CHEM. SOC. 125:940-50).

[0133] In some embodiments, such a reversible modification allows protection during *in vivo* administration (*e.g.*, transit through the blood and/or lysosomal/endosomal compartments of a cell) where the oligonucleotide will be exposed to nucleases and other harsh environmental conditions (*e.g.*, pH). When released into the cytosol of a cell where the levels of glutathione are higher compared to extracellular space, the modification is reversed, and the result is a cleaved oligonucleotide. Using reversible, glutathione-sensitive moieties, it is possible to introduce sterically larger chemical groups into the oligonucleotide of interest when compared to the options available using irreversible chemical modifications. This is because these larger chemical groups will be removed in the cytosol and, therefore, should not interfere with the biological activity of the oligonucleotides inside the cytosol of a cell. As a result, these larger chemical groups can be engineered to confer various advantages to the nucleotide or oligonucleotide, such as nuclease resistance, lipophilicity, charge, thermal stability, specificity and reduced immunogenicity. In some embodiments, the structure of the glutathione-sensitive moiety can be engineered to modify the kinetics of its release.

[0134] In some embodiments, a glutathione-sensitive moiety is attached to the sugar of the nucleotide. In some embodiments, a glutathione-sensitive moiety is attached to the 2'-carbon of the sugar of a modified nucleotide. In some embodiments, the glutathione-sensitive moiety is located at the 5'-carbon of a sugar, particularly when the modified nucleotide is the 5'-terminal nucleotide of the oligonucleotide. In some embodiments, the glutathione-sensitive moiety is located at the 3'-carbon of sugar, particularly when the modified nucleotide is the 3'-

terminal nucleotide of the oligonucleotide. In some embodiments, the glutathione-sensitive moiety comprises a sulfonyl group. *See, e.g.*, US Provisional Patent Application No. 62/378,635, entitled *Compositions Comprising Reversibly Modified Oligonucleotides and Uses Thereof*, which was filed on August 23, 2016.

vi. Targeting Ligands

[0135] In some embodiments, it is desirable to target the oligonucleotides of the disclosure to one or more cells or one or more organs. Such a strategy can help to avoid undesirable effects in other organs or avoid undue loss of the oligonucleotide to cells, tissue or organs that would not benefit from the oligonucleotide. Accordingly, in some embodiments, oligonucleotides disclosed herein are modified to facilitate targeting and/or delivery to a tissue, cell or organ (*e.g.*, to facilitate delivery of the oligonucleotide to the liver). In certain embodiments, oligonucleotides disclosed herein are modified to facilitate delivery of the oligonucleotide to the hepatocytes of the liver. In some embodiments, an oligonucleotide comprises at least one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6 or more nucleotides) conjugated to one or more targeting ligand(s).

[0136] In some embodiments, the targeting ligand comprises a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein or part of a protein (*e.g.*, an antibody or antibody fragment), or lipid. In some embodiments, the targeting ligand is an aptamer. For example, a targeting ligand may be an RGD peptide that is used to target tumor vasculature or glioma cells, CREKA peptide to target tumor vasculature or stoma, transferring, lactoferrin, or an aptamer to target transferrin receptors expressed on CNS vasculature, or an anti-EGFR antibody to target EGFR on glioma cells. In certain embodiments, the targeting ligand is one or more GalNAc moieties.

[0137] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, 2 to 4 nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (*e.g.*, targeting ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the targeting ligands resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. For example, an oligonucleotide may comprise a stem-loop at either the 5' or 3' end of the sense strand and 1, 2, 3 or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand. In some embodiments, an oligonucleotide (*e.g.*, a ds oligonucleotide) provided by the disclosure comprises a stem-loop at the 3' end of the sense strand, wherein the loop of the stem-

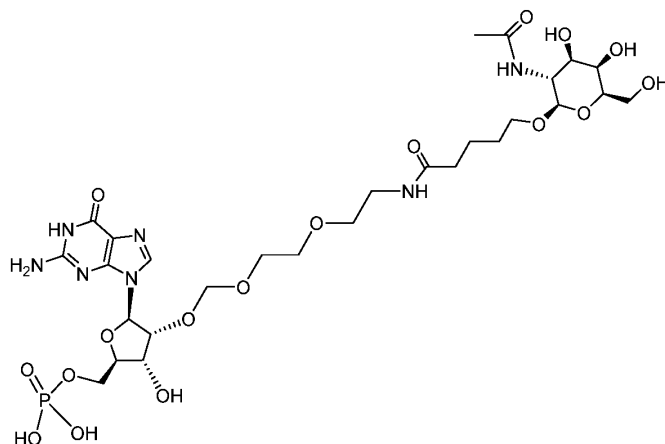
loop comprises a triloop or a tetraloop, and wherein the 3 or 4 nucleotides comprising the triloop or tetraloop, respectfully, are individually conjugated to a targeting ligand.

[0138] GalNAc is a high affinity ligand for the ASGPR, which is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to oligonucleotides of the instant disclosure can be used to target these oligonucleotides to the ASGPR expressed on cells. In some embodiments, an oligonucleotide of the instant disclosure is conjugated to at least one or more GalNAc moieties, wherein the GalNAc moieties target the oligonucleotide to an ASGPR expressed on human liver cells (*e.g.* human hepatocytes). In some embodiments, the GalNAc moiety target the oligonucleotide to the liver.

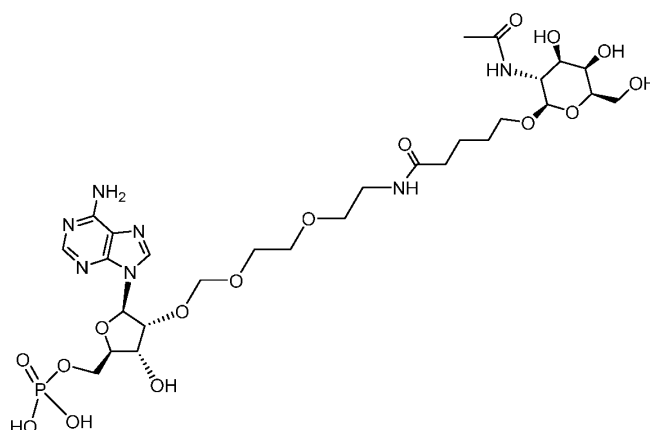
[0139] In some embodiments, an oligonucleotide of the instant disclosure is conjugated directly or indirectly to a monovalent GalNAc. In some embodiments, the oligonucleotide is conjugated directly or indirectly to more than one monovalent GalNAc (*i.e.*, is conjugated to 2, 3 or 4 monovalent GalNAc moieties, and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, an oligonucleotide is conjugated to one or more bivalent GalNAc, trivalent GalNAc or tetravalent GalNAc moieties.

[0140] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a GalNAc moiety. In some embodiments, 2 to 4 nucleotides of a tetraloop are each conjugated to a separate GalNAc. In some embodiments, 1 to 3 nucleotides of a triloop are each conjugated to a separate GalNAc. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (*e.g.*, ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. In some embodiments, GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, 4 GalNAc moieties can be conjugated to nucleotides in the tetraloop of the sense strand where each GalNAc moiety is conjugated to 1 nucleotide.

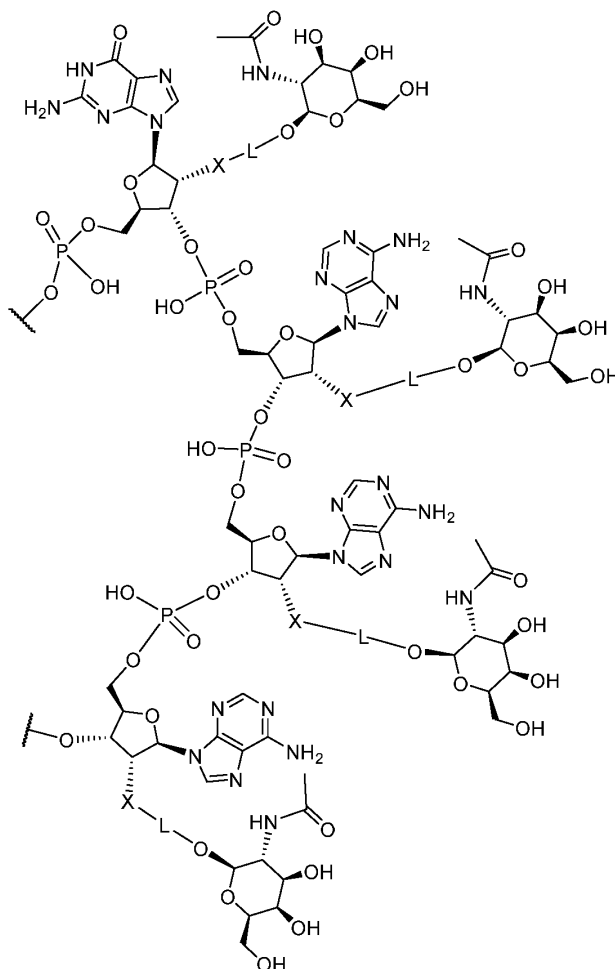
[0141] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to a guanine nucleotide referred to as [ademG-GalNAc] or 2'-aminodiethoxymethanol-Guanine-GalNAc, as depicted below:



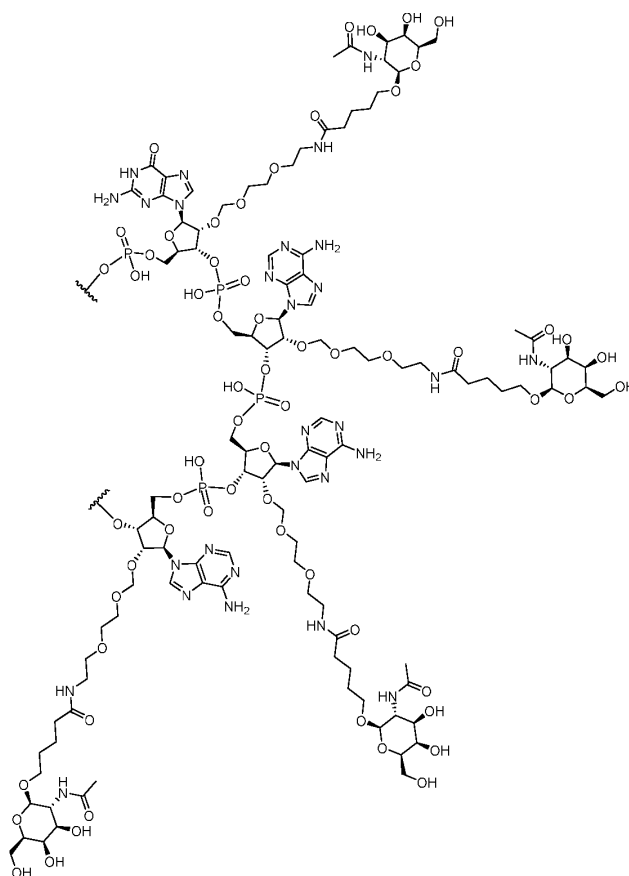
[0142] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2'-aminodiethoxymethanol-Adenine-GalNAc, as depicted below:



[0143] An example of such conjugation is shown below for a loop comprising from 5' to 3' the nucleotide sequence GAAA (L = linker, X = heteroatom) stem attachment points are shown. Such a loop may be present, for example, at positions 27-30 of the sense strand listed in **Table 5** and as shown in **FIG. 3**. In the chemical formula, $\frac{3}{2}$ is used to describe an attachment point to the oligonucleotide strand.



[0144] Appropriate methods or chemistry (e.g., click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is stable. An example is shown below for a loop comprising from 5' to 3' the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker. Such a loop may be present, for example, at positions 27-30 of the any one of the sense strand listed in **Tables 3 or 4** and as shown in **FIG. 10**. In the chemical formula,  is an attachment point to the oligonucleotide strand.



[0145] As mentioned, various appropriate methods or chemistry synthetic techniques (*e.g.*, click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is a stable linker.

[0146] In some embodiments, a duplex extension (*e.g.*, of up to 3, 4, 5 or 6 bp in length) is provided between a targeting ligand (*e.g.*, a GalNAc moiety) and a ds oligonucleotide. In some embodiments, the oligonucleotides herein do not have a GalNAc conjugated thereto.

III. Formulations

[0147] Various formulations have been developed to facilitate oligonucleotide use. For example, oligonucleotides can be delivered to a subject or a cellular environment using a formulation that minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, an oligonucleotide is formulated in buffer solutions such as phosphate buffered saline solutions, liposomes, micellar structures and capsids.

[0148] Formulations of oligonucleotides with cationic lipids can be used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (*e.g.*, polylysine, can be used. Suitable lipids include Oligofectamine, Lipofectamine (Life Technologies), NC388 (Ribozyne Pharmaceuticals, Inc., Boulder, Colo.), or FuGene 6 (Roche) all of which can be used according to the manufacturer's instructions.

[0149] Accordingly, in some embodiments, a formulation comprises a lipid nanoparticle. In some embodiments, an excipient comprises a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere or a nanoparticle, or may be otherwise formulated for administration to the cells, tissues, organs, or body of a subject in need thereof (*see, e.g.*, Remington: THE SCIENCE AND PRACTICE OF PHARMACY, 22nd edition, Pharmaceutical Press, 2013).

[0150] In some embodiments, the formulations herein comprise an excipient. In some embodiments, an excipient confers to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (*e.g.*, sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.*, a buffered solution, petrolatum, dimethyl sulfoxide or mineral oil). In some embodiments, an oligonucleotide is lyophilized for extending its shelf-life and then made into a solution before use (*e.g.*, administration to a subject). Accordingly, an excipient in a composition comprising any one of the oligonucleotides described herein may be a lyoprotectant (*e.g.*, mannitol, lactose, polyethylene glycol or polyvinylpyrrolidone) or a collapse temperature modifier (*e.g.*, dextran, Ficoll™ or gelatin).

[0151] In some embodiments, a pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral (*e.g.*, intravenous, intramuscular, intraperitoneal, intradermal, subcutaneous), oral (*e.g.*, inhalation), transdermal (*e.g.*, topical), transmucosal and rectal administration.

[0152] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Sterile injectable solutions can be prepared by incorporating the oligonucleotides in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[0153] In some embodiments, a composition may contain at least about 0.1% of the therapeutic agent or more, although the percentage of the active ingredient(s) may be between about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

[0154] Even though several embodiments are directed to liver-targeted delivery of any of the oligonucleotides herein, targeting of other tissues is also contemplated.

IV. Methods of Use

i. Reducing *LPA* Expression in Cells

[0155] The disclosure provides methods for contacting or delivering to a cell or population of cells an effective amount any of the oligonucleotides (*e.g.*, a ds oligonucleotide) herein for purposes of reducing *LPA* expression. In some embodiments, a reduction of *LPA* expression is determined by measuring a reduction in the amount or level of *LPA* mRNA, apo(a) protein, or apo(a) activity in a cell. The methods can include the steps described herein, and these may be, but not necessarily, carried out in the sequence as described. Other sequences, however, also are conceivable. Moreover, individual or multiple steps may be carried out either in parallel and/or overlapping in time and/or individually or in multiply repeated steps. Furthermore, the methods may include additional, unspecified steps.

[0156] Methods herein are useful in any appropriate cell type. In some embodiments, a cell is any cell that expresses mRNA (*e.g.*, hepatocytes, macrophages, monocyte-derived cells,

prostate cancer cells, cells of the brain, endocrine tissue, bone marrow, lymph nodes, lung, gall bladder, liver, duodenum, small intestine, pancreas, kidney, gastrointestinal tract, bladder, adipose and soft tissue and skin). In some embodiments, the cell is a primary cell obtained from a subject. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains its natural phenotypic properties. In some embodiments, a cell to which the oligonucleotide is delivered is *ex vivo* or *in vitro* (*i.e.*, can be delivered to a cell in culture or to an organism in which the cell resides).

[0157] In some embodiments, the oligonucleotides herein are delivered to a cell or population of cells using a nucleic acid delivery method known in the art including, but not limited to, injection of a solution containing the oligonucleotide, bombardment by particles covered by the oligonucleotide, exposing the cell or population of cells to a solution containing the oligonucleotide, or electroporation of cell membranes in the presence of the oligonucleotide. Other methods known in the art for delivering oligonucleotides to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[0158] In some embodiments, reduction of *LPA* expression is determined by an assay or technique that evaluates one or more molecules, properties or characteristics of a cell or population of cells associated with *LPA* expression (*e.g.*, using an *LPA* expression biomarker) or by an assay or technique that evaluates molecules that are directly indicative of *LPA* expression in a cell or population of cells (*e.g.*, *LPA* mRNA or apo(a) protein). In some embodiments, the extent to which an oligonucleotide herein reduces *LPA* expression is evaluated by comparing *LPA* expression in a cell or population of cells contacted with the oligonucleotide to a control cell or population of cells (*e.g.*, a cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide). In some embodiments, a control amount or level of *LPA* expression in a control cell or population of cells is predetermined, such that the control amount or level need not be measured in every instance the assay or technique is performed. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

[0159] In some embodiments, contacting or delivering an oligonucleotide (*e.g.*, a ds oligonucleotide) herein to a cell or a population of cells results in a reduction in *LPA* expression. In some embodiments, the reduction in *LPA* expression is relative to a control amount or level of *LPA* expression in cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide. In some embodiments, the

reduction in *LPA* expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of *LPA* expression. In some embodiments, the control amount or level of *LPA* expression is an amount or level of *LPA* mRNA and/or apo(a) protein in a cell or population of cells that has not been contacted with an oligonucleotide herein. In some embodiments, the effect of delivery of an oligonucleotide to a cell or population of cells according to a method herein is assessed after any finite period or amount of time (*e.g.*, minutes, hours, days, weeks, months). For example, in some embodiments, *LPA* expression is determined in a cell or population of cells at least about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 24 hours; or at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, about 56 days, about 63 days, about 70 days, about 77 days, or about 84 days or more after contacting or delivering the oligonucleotide to the cell or population of cells. In some embodiments, *LPA* expression is determined in a cell or population of cells at least about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months or more after contacting or delivering the oligonucleotide to the cell or population of cells.

[0160] In some embodiments, an oligonucleotide is delivered in the form of a transgene that is engineered to express in a cell the oligonucleotide or strands comprising the oligonucleotide (*e.g.*, its sense and antisense strands). In some embodiments, an oligonucleotide is delivered using a transgene engineered to express any oligonucleotide disclosed herein. Transgenes may be delivered using viral vectors (*e.g.*, adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus or herpes simplex virus) or non-viral vectors (*e.g.*, plasmids or synthetic mRNAs). In some embodiments, transgenes can be injected directly to a subject.

ii. Medical Use

[0161] The disclosure also provides oligonucleotides for use, or adaptable for use, to treat a subject (*e.g.*, a human having a disease, disorder or condition associated with *LPA* expression) that would benefit from reducing *LPA* expression. In some embodiments, the disclosure provides oligonucleotides for use, or adapted for use, to treat a subject having a disease, disorder or condition associated with expression of *LPA*. The disclosure also provides oligonucleotides for use, or adaptable for use, in the manufacture of a medicament or

pharmaceutical composition for treating a disease, disorder or condition associated with *LPA* expression. In some embodiments, the oligonucleotides for use, or adaptable for use, target *LPA* mRNA and reduce *LPA* expression (*e.g.*, *via* the RNAi pathway). In some embodiments, the oligonucleotides for use, or adaptable for use, target *LPA* mRNA and reduce the amount or level of *LPA* mRNA, apo(a) protein and/or apo (a) activity.

[0162] In addition, in some embodiments of the methods herein, a subject having a disease, disorder or condition associated with *LPA* expression or is predisposed to the same is selected for treatment with an oligonucleotide (*e.g.*, a ds oligonucleotide) herein. In some embodiments, the method comprises selecting an individual having a marker (*e.g.*, a biomarker) for a disease, disorder or condition associated with *LPA* expression, or predisposed to the same, such as, but not limited to, *LPA* mRNA, apo(a) protein, lipoprotein(a), or a combination thereof. Likewise, and as detailed below, some embodiments of the methods provided by the disclosure include steps such as measuring or obtaining a baseline value for a marker of *LPA* expression (*e.g.*, lipoprotein(a)), and then comparing such obtained value to one or more other baseline values or values obtained after the subject is administered the oligonucleotide to assess the effectiveness of treatment.

iii. Methods of Treatment

[0163] The disclosure also provides methods of treating a subject having, suspected of having, or at risk of developing a disease, disorder or condition associated with *LPA* expression with an oligonucleotide herein. In some embodiments, the disclosure provides methods of treating or attenuating the onset or progression of a disease, disorder or condition associated with *LPA* expression using the oligonucleotides herein. In other embodiments, the disclosure provides methods to achieve one or more therapeutic benefits in a subject having a disease, disorder or condition associated with *LPA* expression using the oligonucleotides herein. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of any one or more of the oligonucleotides herein. In some embodiments, treatment comprises reducing *LPA* expression. In some embodiments, the subject is treated therapeutically. In some embodiments, the subject is treated prophylactically.

[0164] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that *LPA* expression is reduced in the subject, thereby treating the subject. In some embodiments, an amount or level of *LPA* mRNA is reduced in the subject. In some embodiments, an amount or level of apo(a) protein is reduced in the subject. In some embodiments, an amount or level of

lipoprotein(a) is reduced in the subject. In some embodiments, an amount or level of apo(a) activity is reduced in the subject. In some embodiments, an amount or level of triglyceride (TG) (*e.g.*, one or more TG(s) or total TGs) is reduced in the subject. In some embodiments, an amount or level of cholesterol (*e.g.*, total cholesterol, LDL cholesterol, and/or HDL cholesterol) is reduced in the subject. In some embodiments, an amount or level of low-density lipoprotein (LDL) cholesterol is reduced in the subject. In some embodiments, an amount or activity of OxPL is reduced or altered in the subject. In some embodiments, an amount or activity of LDL-C is reduced or altered in the subject. In some embodiments, an amount or activity of apoB-100 is reduced or altered in the subject. In some embodiments, any combination of the following is reduced or altered in the subject: *LPA* expression, an amount or level of *LPA* mRNA, an amount or level of apo(a) protein, an amount or level of apo(a) activity, an amount or level of TG, an amount or level of cholesterol, an amount or activity of OxPL, an amount or activity of LDL-C, and/or an amount or activity of apoB-100.

[0165] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that *LPA* expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to *LPA* expression prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, *LPA* expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to *LPA* expression in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0166] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that an amount or level of *LPA* mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of *LPA* mRNA prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of *LPA* mRNA is reduced in the

subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of *LPA* mRNA in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0167] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that an amount or level of apo(a) protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of apo(a) protein prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of apo(a) protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of apo(a) protein in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0168] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that an amount or level of apo(a) activity is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of apo(a) activity prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of apo(a) activity is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of apo(a) activity in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0169] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that an amount or level of lipoprotein(a) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of lipoprotein(a) prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of lipoprotein(a) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of lipoprotein(a) in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0170] Lipoprotein(a) levels range widely in human adults with plasma levels ranging from <0.1 mg/dL to >200 mg/dL, thus exhibiting up to three orders of magnitude difference among individuals (Schmidt et al., (2016) *J Lipid Res.* 57(8):1339-1359). Lipoprotein(a) levels <30 mg/dl are considered optimal in the United States and Canada (Anderson et al., (2016) *CAN J CARDIOL* 32:1263-82). The European Atherosclerosis Society (EAS) has proposed <50 mg/dL as optimal, and lipoprotein(a) levels >60 mg/dl are used as a cutoff for the reimbursement of apheresis in Germany and the United Kingdom (Tsimikas (2017) *J AM COLL CARDIOL.* 69(6):692-711). In some embodiments, a subject selected for treatment or treated with an oligonucleotide herein is identified or determined to have an amount or level of lipoprotein(a) of about 30 mg/dL or greater. In some embodiments, a subject selected for treatment or treated with an oligonucleotide herein is identified or determined to have an amount or level of lipoprotein(a) of >30 mg/dL. In some embodiments, a subject selected for treatment or treated with an oligonucleotide herein is identified or determined to have an amount or level of lipoprotein(a) of about 50 mg/dL or greater. In some embodiments, a subject selected for treatment or treated with an oligonucleotide herein is identified or determined to have an amount or level of lipoprotein(a) of about 60 mg/dL or greater. In some embodiments, a subject selected for treatment or treated with an oligonucleotide herein is identified or determined to have an amount or level of lipoprotein(a) in the range of 30 mg/dL to 300 mg/dL.

[0171] Generally, a normal or desirable TG range for a human patient is <150mg/dL of blood, with <100 being considered ideal. In some embodiments, the patient selected for

treatment or treated is identified or determined to have an amount or level of TG of ≥ 150 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG in the range of 150 to 199 mg/dL, which is considered borderline high TG levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG in the range of 200 to 499 mg/dL, which is considered high TG levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG in the range of 500 mg/dL or higher (i.e., ≥ 500 mg/dL), which is considered very high TG levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG which is ≥ 150 mg/dL, ≥ 200 mg/dL or ≥ 500 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG of 200 to 499 mg/dL, or 500 mg/dL or higher. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of TG which is ≥ 200 mg/dL.

[0172] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *LPA* expression such that an amount or level of cholesterol (*e.g.*, total cholesterol, LDL cholesterol, and/or HDL cholesterol) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of cholesterol prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of cholesterol is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of cholesterol in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0173] Generally, a normal or desirable cholesterol range (total cholesterol) for an adult human patient is < 200 mg/dL of blood. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol of ≥ 200 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol in the range of 200 to 239 mg/dL, which is considered borderline high cholesterol levels. In some embodiments, the patient selected for treatment or

treated is identified or determined to have an amount or level of cholesterol in the range of 240mg/dL and higher (i.e., ≥ 240 mg/dL), which is considered high cholesterol levels. In some embodiments, the patient selected from treatment or treated is identified or determined to have an amount or level of cholesterol of 200 to 239 mg/dL, or 240mg/dL or higher. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol which is ≥ 200 mg/dL or ≥ 240 mg/dL or higher.

[0174] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder, or condition associated with *LPA* expression such that an amount or level of LDL cholesterol is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of LDL cholesterol prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of LDL cholesterol is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of LDL cholesterol in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[0175] Generally, a normal or desirable LDL cholesterol range for an adult human patient is <100 mg/dL of blood. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of cholesterol of ≥ 100 mg/dL. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of LDL cholesterol in the range of 100 to 129 mg/dL, which is considered above optimal. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of LDL cholesterol in the range of 130 to 159mg/dL, which is considered borderline high levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of LDL cholesterol in the range of 160 to 189mg/dL, which is considered high LDL cholesterol levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of LDL cholesterol in the range of 190mg/dL and higher (i.e., ≥ 190 mg/dL), which is considered very high LDL cholesterol levels. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of LDL

cholesterol which is $\geq 100\text{mg/dL}$, $\geq 130\text{mg/dL}$, $\geq 160\text{mg/dL}$, or $\geq 190\text{mg/dL}$ or higher, preferably $\geq 160\text{mg/dL}$, or $\geq 190\text{mg/dL}$ or higher. In some embodiments, the patient selected for treatment or treated is identified or determined to have an amount or level of LDL cholesterol of 100 to 129 mg/dL, 130 to 159mg/dL, 160 to 189mg/dL, or 190mg/dL and higher.

[0176] Suitable methods for determining *LPA* expression, an amount or level of *LPA* mRNA, an amount or level of apo(a) protein, an amount or level of apo(a) activity, an amount or level of lipoprotein(a), and/or an amount or level of OxPL, LDL-C, apoB-100, TG and/or LDL cholesterol in the subject, or in a sample from the subject, are known in the art. Further, the Examples set forth herein illustrate exemplary methods for determining *LPA* expression.

[0177] In some embodiments, *LPA* expression, the amount or level of *LPA* mRNA, apo(a) protein, apo(a) activity, OxPL, LDL-C, apoB-100, TG, LDL cholesterol, or any combination thereof, is reduced in a cell (*e.g.*, a hepatocyte), a population or a group of cells (*e.g.*, an organoid), an organ (*e.g.*, liver), blood or a fraction thereof (*e.g.*, plasma), a tissue (*e.g.*, liver tissue), a sample (*e.g.*, a liver biopsy sample), or any other biological material obtained or isolated from the subject. In some embodiments, *LPA* expression, the amount or level of *LPA* mRNA, apo(a) protein, apo(a) activity, OxPL, LDL-C, apoB-100, TG, LDL cholesterol, or any combination thereof, is reduced in more than one type of cell (*e.g.*, a hepatocyte and one or more other type(s) of cell), more than one groups of cells, more than one organ (*e.g.*, liver and one or more other organ(s)), more than one fraction of blood (*e.g.*, plasma and one or more other blood fraction(s)), more than one type of tissue (*e.g.*, liver tissue and one or more other type(s) of tissue), more than one type of sample (*e.g.*, a liver biopsy sample and one or more other type(s) of biopsy sample) obtained or isolated from the subject.

[0178] Examples of a disease, disorder or condition associated with *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, or a combination thereof.

[0179] Because of their high specificity, the oligonucleotides herein specifically target mRNAs of target genes of cells, tissues, or organs (*e.g.*, liver). In preventing disease, the target gene may be one which is required for initiation or maintenance of the disease or which has been identified as being associated with a higher risk of contracting the disease. In treating

disease, the oligonucleotide can be brought into contact with the cells or tissue exhibiting or responsible for mediating the disease. For example, an oligonucleotide substantially identical to all or part of a wild-type (*i.e.*, native) or mutated gene associated with a disorder or condition associated with *LPA* expression may be brought into contact with or introduced into a cell or tissue type of interest such as a hepatocyte or other liver cell.

[0180] In some embodiments, the target gene may be a target gene from any mammal, such as a human. Any gene may be silenced according to the method described herein.

[0181] Methods described herein are typically involve administering to a subject a therapeutically effective amount of an oligonucleotide herein, that is, an amount capable of producing a desirable therapeutic result. A therapeutically acceptable amount may be an amount that can therapeutically treat a disease or disorder. The appropriate dosage for any one subject will depend on certain factors, including the subject's size, body surface area, age, the particular composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other drugs being administered concurrently.

[0182] In some embodiments, a subject is administered any one of the compositions herein either enterally (*e.g.*, orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy or rectally), parenterally (*e.g.*, subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, intrathecal), topically (*e.g.*, epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (*e.g.*, the liver of a subject). Typically, oligonucleotides herein are administered intravenously or subcutaneously.

[0183] As a non-limiting set of examples, the oligonucleotides herein would typically be administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the oligonucleotides may be administered every week or at intervals of two, or three weeks. Alternatively, the oligonucleotides may be administered daily. In some embodiments, a subject is administered one or more loading doses of the oligonucleotide followed by one or more maintenance doses of the oligonucleotide.

[0184] In some embodiments, the subject to be treated is a human or non-human primate or other mammalian subject. Other exemplary subjects include domesticated animals such as dogs and cats; livestock such as horses, cattle, pigs, sheep, goats, and chickens; and animals such as mice, rats, guinea pigs, and hamsters.

V. Kits

[0185] In some embodiments, the disclosure provides a kit comprising an oligonucleotide herein, and instructions for use. In some embodiments, the kit comprises an oligonucleotide herein, and a package insert containing instructions for use of the kit and/or any component thereof. In some embodiments, the kit comprises, in a suitable container, an oligonucleotide herein, one or more controls, and various buffers, reagents, enzymes and other standard ingredients well known in the art. In some embodiments, the container comprises at least one vial, well, test tube, flask, bottle, syringe or other container means, into which the oligonucleotide is placed, and in some instances, suitably aliquoted. In some embodiments where an additional component is provided, the kit contains additional containers into which this component is placed. The kits can also include a means for containing the oligonucleotide and any other reagent in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits can include labeling with instructions for use and/or warnings.

[0186] In some embodiments, a kit comprises an oligonucleotide herein, and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising the oligonucleotide and instructions for treating or delaying progression of a disease, disorder or condition associated with *LPA* expression in a subject in need thereof.

EXAMPLES

[0187] While the disclosure has been described with reference to the specific embodiments set forth in the following Examples, it should be understood by those skilled in the art that various changes may be made, and equivalents may be substituted without departing from the true spirit and scope of the disclosure. Further, the following Examples are offered by way of illustration and are not intended to limit the scope of the disclosure in any manner. In addition, modifications may be made to adapt to a situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the disclosure. All such modifications are intended to be within the scope of the disclosure. Standard techniques well known in the art or the techniques specifically described below are utilized.

Example 1: Preparation of Double-Stranded RNAi Oligonucleotides

[0188] *Oligonucleotide Synthesis and Purification*

[0189] The ds RNAi oligonucleotides described in the foregoing Examples are chemically synthesized using methods described herein. Generally, ds RNAi oligonucleotides are

synthesized using solid phase oligonucleotide synthesis methods as described for 19-23mer siRNAs (*see, e.g.,* Scaringe *et al.* (1990) NUCLEIC ACIDS RES. 18:5433-41 and Usman *et al.* (1987) J. AM. CHEM. SOC. 109:7845-45; *see also*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,008,400; 6,111,086; 6,117,657; 6,353,098; 6,362,323; 6,437,117 and 6,469,158).

[0190] Individual RNA strands are synthesized and HPLC purified according to standard methods (Integrated DNA Technologies; Coralville, IA). For example, RNA oligonucleotides are synthesized using solid phase phosphoramidite chemistry, deprotected and desalted on NAP-5 columns (Amersham Pharmacia Biotech; Piscataway, NJ) using standard techniques (Damha & Olgivie (1993) METHODS MOL. BIOL. 20:81-114; Wincott *et al.* (1995) NUCLEIC ACIDS RES. 23:2677-84). The oligomers are purified using ion-exchange high performance liquid chromatography (IE-HPLC) on an Amersham Source 15Q column (1.0 cm×25 cm; Amersham Pharmacia Biotech) using a 15 min step-linear gradient. The gradient varies from 90:10 Buffers A:B to 52:48 Buffers A:B, where Buffer A is 100 mM Tris pH 8.5 and Buffer B is 100 mM Tris pH 8.5, 1 M NaCl. Samples are monitored at 260 nm and peaks corresponding to the full-length oligonucleotide species are collected, pooled, desalted on NAP-5 columns, and lyophilized.

[0191] The purity of each oligomer is determined by capillary electrophoresis (CE) on a Beckman PACE 5000 (Beckman Coulter, Inc.; Fullerton, CA). The CE capillaries have a 100 µm inner diameter and contain ssDNA 100R Gel (Beckman-Coulter). Typically, about 0.6 nmole of oligonucleotide is injected into a capillary, is run in an electric field of 444 V/cm and is detected by UV absorbance at 260 nm. Denaturing Tris-Borate-7 M-urea running buffer is purchased from Beckman-Coulter. Oligoribonucleotides are obtained that are at least 90% pure as assessed by CE for use in experiments described below. Compound identity is verified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy on a Voyager DE™ Biospectrometry Work Station (Applied Biosystems; Foster City, CA) following the manufacturer's recommended protocol. Relative molecular masses of all oligomers are obtained, often within 0.2% of expected molecular mass.

[0192] *Preparation of Duplexes*

[0193] ssRNA oligomers are resuspended (*e.g.,* at 100 µM concentration) in duplex buffer consisting of 100 mM potassium acetate, 30 mM HEPES, pH 7.5. Complementary sense and antisense strands are mixed in equal molar amounts to yield a final solution of, for example, 50 µM duplex. Samples are heated to 100°C for 5' in RNA buffer (IDT) and are allowed to cool to room temperature before use. The ds RNA oligonucleotides are stored at -20° C. ss RNA oligomers are stored lyophilized or in nuclease-free water at -80° C.

Example 2: RNAi Oligonucleotide Inhibition of *LPA* Expression *In Vitro***[0194]** *LPA mRNA Target Sequence Identification*

[0195] To identify RNAi oligonucleotide inhibitors of *LPA* expression, a computer-based algorithm was used to computationally identify *LPA* mRNA target sequences suitable for assaying inhibition of *LPA* expression by the RNAi pathway. The algorithm provides RNAi oligonucleotide guide (antisense) strand sequences each having a region of complementarity to a suitable *LPA* target sequence of human *LPA* mRNA (e.g., SEQ ID NO: 1; **Table 1**). Some of the guide strand sequences identified by the algorithm are also complementary to the corresponding *LPA* target sequence of monkey *LPA* mRNA (SEQ ID NO: 2; **Table 1**). RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) were generated (**Table 2**), each with a unique guide strand having a region of complementarity to an *LPA* target sequence identified by the algorithm. The passenger (sense) strands of the DsiRNAs provided in **Table 2** comprise a unique human *LPA* mRNA target sequence identified by the algorithm.

[0196] **Table 1:** Sequences of Human and NHP (Monkey) mRNA

Species	GenBank Ref Seq #	SEQ ID NO:
Human (Hs)	NM_005577.3	1
Cynomolgus monkey (Mf)	XM_015448517.1	2
Rhesus monkey	XM_028847001.1	3

[0197] **Table 2:** DsiRNAs Targeting Human *LPA* mRNA and Controls Evaluated in Cells

Dsi RNA	Passenger (Sense)	SEQ ID NO:	Guide (Antisense)	SEQ ID NO:	Target Sequence	SEQ ID NO:
LPA - 125	CUGAGCAAAGCCAUGUGGUACAGGA	4	UCCUGUACCACAUGCUCUUGCUCAGGU	404	CUGAGCAAAGCCAUGUGGU	804
LPA - 128	AGCAAAGCCAUGUGGUCCAAGAUTG	5	CAAUCUUGGACCAC AUGGCUUUGCUCA	405	AGCAAAGCCAUGUGGUCCA	805
LPA - 132	AAGCCAUGUGGUCCAGGAUAGCUAC	6	GUAGCUAUCCUGGACCAUGGCUUUG	406	AAGCCAUGUGGUCCAGGAU	806
LPA - 133	AGCCAUGUGGUCCAGGAUUACUACC	7	GGUAGUAAUCCUGGACCACAUGGCUUU	407	AGCCAUGUGGUCCAGGAUU	807
LPA - 134	GCCAUGUGGUCCAGGAUUGAUACCA	8	UGGUAUCAAUCCUGGACCACAUGGCUU	408	GCCAUGUGGUCCAGGAUUG	808
LPA - 135	CCAUGUGGUCCAGGAUUGCAACCAT	9	AUGGUUGCAAUCCUGGACCACAUGGCU	409	CCAUGUGGUCCAGGAUUGC	809
LPA - 136	CAUGUGGUCCAGGAUUGCUACCATG	10	CAUGGUAGCAAUCCUGGACCACAUGGC	410	CAUGUGGUCCAGGAUUGCU	810

LPA - 137	AUGUGGUCCAGGAUUGCUA ACAUGG	11	CCAUGUUAGCAAUC CUGGACCACAUGG	411	AUGUGGUCCA GGAUUGCUA	811
LPA - 138	UGUGGUCCAGGAUUGCUAC AAUGGT	12	ACCAUUGUAGCAAU CCUGGACCACAUG	412	UGUGGUCCAG GAUUGCUAC	812
LPA - 160	GGUGAUGGACAGAGUUAUC AAGGCA	13	UGCCUUGAUAAACUC UGUCCAUCACCAU	413	GGUGAUGGAC AGAGUUAUC	813
LPA - 190	UCCACCACUGUCACAGGAA AGACCT	14	AGGUCUUUCCUGUG ACAGUGGUGGAGU	414	UCCACCACUG UCACAGGAA	814
LPA - 191	CCACCACUGUCACAGGAAG AACCTG	15	CAGGUUCUCCUGU GACAGUGGUGGAG	415	CCACCACUGU CACAGGAAG	815
LPA - 197	CUGUCACAGGAAGGACCUG ACAAGC	16	GCUUGUCAGGUCCU UCCUGUGACAGUG	416	CUGUCACAGG AAGGACCUG	816
LPA - 205	GGAAGGACCUGCCAAGCUU AGUCAT	17	AUGACUAAGCUUGG CAGGUCCUCCUG	417	GGAAGGACCU GCCAAGCUU	817
LPA - 206	GAAGGACCUGCCAAGCUUG AUCATC	18	GAUGAUCAAGCUUG GCAGGUCCUCCU	418	GAAGGACCUG CCAAGCUUG	818
LPA - 208	AGGACCUGCCAAGCUUGGU AAUCTA	19	UAGAUUACCAAGCU UGGCAGGUCCUUC	419	AGGACCUGCC AAGCUUGGU	819
LPA - 209	GGACCUGCCAAGCUUGGUC AUCUAT	20	AUAGAUGACCAAGC UUGGCAGGUCCU	420	GGACCUGCCA AGCUUGGUC	820
LPA - 210	GACCUGCCAAGCUUGGUCA ACUATG	21	CAUAGUUGACCAAG CUUGGCAGGUCCU	421	GACCUGCCAA GCUUGGUCA	821
LPA - 211	ACCUGCCAAGCUUGGUCAU AUAUGA	22	UCAUAUAUGACCAA GCUUGGCAGGUCC	422	ACCUGCCAAG CUUGGUCAU	822
LPA - 212	CCUGCCAAGCUUGGUCAUC AAUGAC	23	GUCAUUGAUGACCA AGCUUGGCAGGUC	423	CCUGCCAAGC UUGGUCAUC	823
LPA - 219	AGCUUGGUCAUCUAUGACA ACACAT	24	AUGUGUUGUCAUAG AUGACCAAGCUUG	424	AGCUUGGUCA UCUAUGACA	824
LPA - 225	GUCAUCUAUGACACCACAU AAACAT	25	AUGUUUAUGUGGUG UCAUGAUGACCA	425	GUCAUCUAUG ACACCACAU	825
LPA - 258	CACAGAAAACUACCCAAAU ACUGGC	26	GCCAGUAUUUGGGU AGUUUUCUGUGGU	426	CACAGAAAAC UACCCAAAU	826
LPA - 261	AGAAAACUACCCAAAUUGCU AGCUTG	27	CAAGCUAGCAUUUG GGUAGUUUUCUGU	427	AGAAAACUAC CCAAUUGCU	827
LPA - 263	AAAACUACCCAAAUUGCUGG AUUGAT	28	AUCAAUCCAGCAUU UGGGUAGUUUUCU	428	AAAACUACCC AAUUGCUGG	828
LPA - 269	ACCCAAAUUGCUGGCUUGAU AAUGAA	29	UUCAUUUAUCAAGCC AGCAUUUGGGUAG	429	ACCCAAAUGC UGGCUUGAU	829
LPA - 270	CCCAAUUGCUGGCUUGAUC AUGAAC	30	GUUCAUGAUCAGC CAGCAUUUGGGUA	430	CCCAAUUGCU GGCUUGAUC	830

LPA - 291	GAACUACUGCAGGAAUCCA AAUGCT	31	AGCAUUGGAUUC UGCAGUAGUUAU	431	GAACUACUGC AGGAAUCCA	831
LPA - 295	UACUGCAGGAAUCCAGAUG AUGUGG	32	CCACAUCAUCUGGA UUCUGCAGUAGU	432	UACUGCAGGA AUCCAGAUG	832
LPA - 296	ACUGCAGGAAUCCAGAUGC AGUGGC	33	GCCACUGCAUCUGG AUUCUGCAGUAG	433	ACUGCAGGAA UCCAGAUGC	833
LPA - 298	UGCAGGAAUCCAGAUGCUG AGGCAG	34	CUGCCUCAGCAUCU GGAUUCUGCAGU	434	UGCAGGAAUC CAGAUGCUG	834
LPA - 355	AGGUGGGAGUACUGCAACC AGACGC	35	GCGUCUGGUUGCAG UACUCCCACCUGA	435	AGGUGGGAGU ACUGCAACC	835
LPA - 380	AAUGCUCAGACGCAGAAGG AACUGC	36	GCAGUCCUUCUGC GUCUGAGCAUUGC	436	AAUGCUCAGA CGCAGAAGG	836
LPA - 417	GACUGUUACCCCGGUUCCA AGCCTA	37	UAGGCUUGGAACCG GGGUAACAGUCGG	437	GACUGUUACC CCGGUUCCA	837
LPA - 418	ACUGUUACCCCGGUUCCAA ACCUAG	38	CUAGGUUUGGAACC GGGUAAACAGUCG	438	ACUGUUACCC CGGUUCCAA	838
LPA - 419	CUGUUACCCCGGUUCCAAG ACUAGA	39	UCUAGUCUUGGAAC CGGGUAAACAGUC	439	CUGUUACCCC GGUUCCAAG	839
LPA - 420	UGUUACCCCGGUUCCAAGC AUAGAG	40	CUCUAUGCUUGGAA CCGGGUAAACAGU	440	UGUUACCCCG GUUCCAAGC	840
LPA - 421	GUUACCCCGGUUCCAAGCC AAGAGG	41	CCUCUUGGCUUGGA ACCGGGUAAACAG	441	GUUACCCCGG UUCCAAGCC	841
LPA - 422	UUACCCCGGUUCCAAGCCU AGAGGC	42	GCCUCUAGGCUUGG AACC GG GUAAACA	442	UUACCCCGGU UCCAAGCCU	842
LPA - 423	UACCCCGGUUCCAAGCCUA AAGGCT	43	AGCCUUUAGGCUUG GAACCGGGUAAAC	443	UACCCCGGUU CCAAGCCUA	843
LPA - 492	GUGCUACCAUGGUAAUGGA AAGAGT	44	ACUCUUUCCAUIAC CAUGGUAGCACUC	444	GUGCUACCAU GGUAAUGGA	844
LPA - 493	UGCUACCAUGGUAAUGGAC AGAGTT	45	AACUCUGUCCAUIA CCAUGGUAGCACU	445	UGCUACCAUG GUAAUGGAC	845
LPA - 494	GCUACCAUGGUAAUGGACA AAGUTA	46	UAACUUUGUCCAUI ACCAUGGUAGCAC	446	GCUACCAUGG UAAUGGACA	846
LPA - 495	CUACCAUGGUAAUGGACAG AGUUAT	47	AUAACUCUGUCCAUI UACCAUGGUAGCA	447	CUACCAUGGU AAUGGACAG	847
LPA - 496	UACCAUGGUAAUGGACAGA AUUATC	48	GAUAAUUCUGUCCA UUACCAUGGUAGC	448	UACCAUGGUA AUGGACAGA	848
LPA - 497	ACCAUGGUAAUGGACAGAG AUAUCG	49	CGAUUUCUCUGUCC AUUACCAUGGUAG	449	ACCAUGGUAA UGGACAGAG	849
LPA - 498	CCAUGGUAAUGGACAGAGU AAUCGA	50	UCGAUUAUCUCUGUC CAUUAACCAUGGUA	450	CCAUGGUAAU GGACAGAGU	850

LPA - 499	CAUGGUAUUGGACAGAGUU AUCGAG	51	CUCGAUAAACUCUGU CCAUUACCAUGGU	451	CAUGGUAUUGG GACAGAGUU	851
LPA - 500	AUGGUAUUGGACAGAGUUA ACGAGG	52	CCUCGUUAAACUCUG UCCAUUACCAUGG	452	AUGGUAUUGG ACAGAGUUA	852
LPA - 501	UGGUAUUGGACAGAGUUAU AGAGGC	53	GCCUCUAUAAACUCU GUCCAUUACCAUG	453	UGGUAUUGGA CAGAGUUAU	853
LPA - 502	GGUAAUUGGACAGAGUUUUC AAGGCA	54	UGCCUUGAUAAACUC UGUCCAUUACCAU	454	GGUAAUUGGAC AGAGUUUUC	854
LPA - 503	GUAUUGGACAGAGUUUUCG AGGCAC	55	GUGCCUCGAUAAACU CUGUCCAUUACCA	455	GUAUUGGACA GAGUUUUCG	855
LPA - 523	GGCACAUAUCCACCACUG ACACAG	56	CUGUGUCAGUGGUG GAGUAUGUGCCUC	456	GGCACAUAU CCACCACUG	856
LPA - 563	CUUGGUCAUCUAUGACACC ACACTC	57	GAGUGUGGUGUCAU AGAUGACCAAGCU	457	CUUGGUCAUC UAUGACACC	857
LPA - 567	GUCAUCUAUGACACCACAC ACGCAT	58	AUGCGUGUGUGGUG UCAUAGAUGACCA	458	GUCAUCUAUG ACACCACAC	858
LPA - 568	UCAUCUAUGACACCACACU AGCATA	59	UAUGCUAGUGUGGU GUCAUAGAUGACC	459	UCAUCUAUGA CACCACACU	859
LPA - 569	CAUCUAUGACACCACACUC ACAUAG	60	CUAUGUGAGUGUGG UGUCAUAGAUGAC	460	CAUCUAUGAC ACCACACUC	860
LPA - 120 8	GCACAUACUCCACCACUGU AACUGG	61	CCAGUUACAGUGGU GGAGUAUGUGCCU	461	GCACAUACUC CACCACUGU	861
LPA - 271 5	AGCCCCUUAUUGUUUACG AGGGAT	62	AUCCUCGUUUAAC AAUAAGGGGCGC	462	AGCCCCUUAU UGUUUACG	862
LPA - 271 6	GCCCCUUAUUGUUUACGA AGGATC	63	GAUCCUUCGUUUA CAAUAAGGGGCGC	463	GCCCCUUAU GUUUAACGA	863
LPA - 282 7	CCAAGCCUAGAGGCUCCUU AUGAAC	64	GUUCAUAAGGAGCC UCUAGGCUUGGAA	464	CCAAGCCUAG AGGCUCCUU	864
LPA - 283 7	AGGCUCCUUCUGAACAGC ACCAAC	65	GUUGGUGCUUGUUC AGAAGGAGCCUCU	465	AGGCUCCUUC UGAACAGC	865
LPA - 290 0	AUGGACAGAGUUUUAAGG AACATA	66	UAUGUUCUUGAU ACUCUGUCCAUUU	466	AUGGACAGAG UUUAAGG	866
LPA - 290 1	UGGACAGAGUUUUAAGGC ACAUAC	67	GUAUGUGCCUUGAU AACUCUGUCCAUU	467	UGGACAGAGU UAUAAGGC	867

LPA - 290 2	GGACAGAGUUAUCAAGGCACA AAUACT	68	AGUAUUUGCCUUGA UAACUCUGUCCA	468	GGACAGAGUU AUCAAGGCA	868
LPA - 290 3	GACAGAGUUAUCAAGGCAC AUACTT	69	AAGUAUGUGCCUUG AUAACUCUGUCCA	469	GACAGAGUUA UCAAGGCAC	869
LPA - 290 4	ACAGAGUUAUCAAGGCACA AACUTC	70	GAAGUUUGUGCCUU GAUAACUCUGUCC	470	ACAGAGUUUA CAAGGCACA	870
LPA - 290 5	CAGAGUUAUCAAGGCACAU ACUUCA	71	UGAAGUAUGUGCCU UGAUAACUCUGUC	471	CAGAGUUAUC AAGGCACAU	871
LPA - 300 4	UACCCAAUUGCUGGCCUUGA ACAAGA	72	UCUUGUUAAGCCA GCAUUUGGUAGU	472	UACCCAAUUG CUGGCCUUGA	872
LPA - 300 7	CCAAUUGCUGGCCUUGAUCA AGAACT	73	AGUUCUUGAUCAAG CCAGCAUUUGGGU	473	CCAAUUGCUG GCUUGAUCA	873
LPA - 302 3	UCAAGAACUACUGCCGAAA ACCAGA	74	UCUGGUUUUCGGCA GUAGUUCUUGAUC	474	UCAAGAACUA CUGCCGAAA	874
LPA - 302 4	CAAGAACUACUGCCGAAAU ACAGAT	75	AUCUGUAUUUCGGC AGUAGUUCUUGAU	475	CAAGAACUAC UGCCGAAAU	875
LPA - 302 5	AAGAACUACUGCCGAAAU AAGATC	76	GAUCUUGAUUUUCGG CAGUAGUUCUUGA	476	AAGAACUACU GCCGAAAU	876
LPA - 302 7	GAACUACUGCCGAAAUCCA AAUCCCT	77	AGGAUUUGGAUUUC GGCAGUAGUUCUU	477	GAACUACUGC CGAAAUCCA	877
LPA - 303 0	CUACUGCCGAAAUCCAGAU ACUGTG	78	CACAGUAUCUGGAU UUCGGCAGUAGUU	478	CUACUGCCGA AAUCCAGAU	878
LPA - 305 1	UGUGGCAGCCCCUUGGUGU AAUACA	79	UGUAUUACACCAAG GGGCUGCCACAGG	479	UGUGGCAGCC CCUUGGUGU	879
LPA - 305 2	GUGGCAGCCCCUUGGUGUU AUACAA	80	UUGUAUAACACCAA GGGCUGCCACAG	480	GUGGCAGCCC CUUGGUGUU	880
LPA - 305 3	UGGCAGCCCCUUGGUGUUA AACAAC	81	GUUGUUUAACACCA AGGGCUGCCACA	481	UGGCAGCCCC UUGGUGUUA	881
LPA - 305 4	GGCAGCCCCUUGGUGUUAU ACAACA	82	UGUUGUAUAACACC AAGGGCUGCCAC	482	GGCAGCCCCU UGGUGUUAU	882

LPA - 305 5	GCAGCCCCUUGGUGUUUAU AAACAG	83	CUGUUUUUAUACAC CAAGGGGCUGCCA	483	GCAGCCCCU GGUGUUUAU	883
LPA - 305 6	CAGCCCCUUGGUGUUUAUAC AACAGA	84	UCUGUGUAUAACA CCAAGGGGCUGCC	484	CAGCCCCUUG GUGUUUAUAC	884
LPA - 305 7	AGCCCCUUGGUGUUUAUACA ACAGAT	85	AUCUGUUGUAUAAC ACCAAGGGGCUGC	485	AGCCCCUUGG UGUUUAUACA	885
LPA - 305 8	GCCCCUUGGUGUUUAUACAA AAGATC	86	GAUCUUUUGUAUAA CACCAAGGGGCUG	486	GCCCCUUGGU GUUAUACAA	886
LPA - 305 9	CCCCUUGGUGUUUAUACAAC AGAUC	87	GGAUCUGUUGUAUA ACACCAAGGGGCU	487	CCCCUUGGUG UUUAUACAAC	887
LPA - 309 2	GGUGGGAGUACUGCAACCU AACACG	88	CGUGUUAGGUUGCA GUACUCCACCUG	488	GGUGGGAGUA CUGCAACCU	888
LPA - 309 3	GUGGGAGUACUGCAACCU ACACGA	89	UCGUGUCAGGUUGC AGUACUCCACCUG	489	GUGGGAGUAC UGCAACCU	889
LPA - 309 6	GGAGUACUGCAACCU AGAUGC	90	GCAUCUUGUCAGGU UGCAGUACUCCA	490	GGAGUACUGC AACCUGACA	890
LPA - 309 7	GAGUACUGCAACCU AAUGCT	91	AGCAUUGUGUCAGG UUGCAGUACUCCC	491	GAGUACUGCA ACCUGACAC	891
LPA - 309 9	GUACUGCAACCU AGCUCA	92	UGAGCUUCGUGUCA GGUUGCAGUACUC	492	GUACUGCAAC CUGACACGA	892
LPA - 310 0	UACUGCAACCU ACUCAG	93	CUGAGUAUCGUGUC AGGUUGCAGUACU	493	UACUGCAACC UGACACGAU	893
LPA - 310 1	ACUGCAACCU AUCAGA	94	UCUGAUCAUCGUGU CAGGUUGCAGUAC	494	ACUGCAACCU GACACGAUG	894
LPA - 310 2	CUGCAACCU ACAGAT	95	AUCUGUGCAUCGUG UCAGGUUGCAGUA	495	CUGCAACCU ACACGAUGC	895
LPA - 310 3	UGCAACCU AAGATG	96	CAUCUAGCAUCGU GUCAGGUUGCAGU	496	UGCAACCU CACGAUGCU	896
LPA - 310 5	CAACCU AAUGCA	97	UGCAUUGAGCAUC GUGUCAGGUUGCA	497	CAACCU CGAUGCUCA	897

LPA - 310 7	ACCUGACACGAUGCUCAGA AGCAGA	98	UCUGCUUCUGAGCA UCGUGUCAGGUUG	498	ACCUGACACG AUGCUCAGA	898
LPA - 310 8	CCUGACACGAUGCUCAGAU ACAGAA	99	UUCUGUAUCUGAGC AUCGUGUCAGGUU	499	CCUGACACGA UGCUCAGAU	899
LPA - 310 9	CUGACACGAUGCUCAGAU AAGAAT	100	AUUCUUCUUCUGAG CAUCGUGUCAGGU	500	CUGACACGAU GCUCAGAU	900
LPA - 311 0	UGACACGAUGCUCAGAU AGAATG	101	CAUUCUGCAUCUGA GCAUCGUGUCAGG	501	UGACACGAUG CUCAGAU	901
LPA - 311 1	GACACGAUGCUCAGAU AAAUGG	102	CCAUUUUGCAUCUG AGCAUCGUGUCAG	502	GACACGAUGC UCAGAU	902
LPA - 311 2	ACACGAUGCUCAGAU AAUGGA	103	UCCAUCUGCAUCU GAGCAUCGUGUCA	503	ACACGAUGCU CAGAU	903
LPA - 311 3	CACGAUGCUCAGAU AUGGAC	104	GUCCAUCUGCAUC UGAGCAUCGUGUC	504	CACGAUGCUC AGAUGCAGA	904
LPA - 322 9	UGCUACUACCAUUAUGGAC AGAGTT	105	AACUCUGUCCAUA UGGUAGUAGCAGU	505	UGCUACUACC AUUAUGGAC	905
LPA - 323 0	GCUACUACCAUUAUGGACA AAGUTA	106	UAACUUUGUCCAUA AUGGUAGUAGCAG	506	GCUACUACCA UUAUGGACA	906
LPA - 323 1	CUACUACCAUUAUGGACAG AGUUAC	107	GUAACUCUGUCCA AAUGGUAGUAGCA	507	CUACUACCAU UAUGGACAG	907
LPA - 323 2	UACUACCAUUAUGGACAGA AUUACC	108	GGUAAUUCUGUCCA UAAUGGUAGUAGC	508	UACUACCAU AUGGACAGA	908
LPA - 323 3	ACUACCAUUAUGGACAGAG AUACCG	109	CGGUUUCUGUCC AUAAUGGUAGUAG	509	ACUACCAUUA UGGACAGAG	909
LPA - 323 4	CUACCAUUAUGGACAGAGU AACCGA	110	UCGGUUAUCUCUGC CAUAAUGGUAGUA	510	CUACCAUUAU GGACAGAGU	910
LPA - 323 5	UACCAUUAUGGACAGAGUU ACCGAG	111	CUCGGUAAUCUCUG CCAUAUGGUAGU	511	UACCAUUAUG GACAGAGUU	911
LPA - 323 6	ACCAUUAUGGACAGAGUUA ACGAGG	112	CCUCGUUAACUCUG UCCAUAUGGUAG	512	ACCAUUAUGG ACAGAGUUA	912

LPA - 325 7	GAGGCACAUAUCCACCAC AGUCAC	113	GUGACUGUGGUGGA GUAUGUGCCUCGG	513	GAGGCACAUA CUCCACCAC	913
LPA - 326 7	CUCCACCACUGUCACAGGA AGAACT	114	AGUUCUCCUGUGA CAGUGGUGGAGUA	514	CUCCACCACU GUCACAGGA	914
LPA - 328 0	ACAGGAAGAACUUGCCAAG AUUGGT	115	ACCAAUCUUGGCAA GUUCUCCUGUGA	515	ACAGGAAGAA CUUGCCAAG	915
LPA - 328 1	CAGGAAGAACUUGCCAAGC AUGGTC	116	GACCAUGCUUGGCA AGUUCUCCUGUG	516	CAGGAAGAAC UUGCCAAGC	916
LPA - 328 2	AGGAAGAACUUGCCAAGCU AGGUCA	117	UGACCUAGCUUGGC AAGUUCUCCUGU	517	AGGAAGAACU UGCCAAGCU	917
LPA - 328 3	GGAAGAACUUGCCAAGCUU AGUCAT	118	AUGACUAAGCUUGG CAAGUUCUCCUG	518	GGAAGAACUU GCCAAGCUU	918
LPA - 328 4	GAAGAACUUGCCAAGCUUG AUCATC	119	GAUGAUCAGCUUG GCAAGUUCUCCU	519	GAAGAACUUG CCAAGCUUG	919
LPA - 328 5	AAGAACUUGCCAAGCUUGG ACAUCT	120	AGAUGUCCAAGCUU GGCAAGUUCUCC	520	AAGAACUUGC CAAGCUUGG	920
LPA - 328 6	AGAACUUGCCAAGCUUGGU AAUCTA	121	UAGAUUACCAAGCU UGGCAAGUUCUC	521	AGAACUUGCC AAGCUUGGU	921
LPA - 328 7	GAACUUGCCAAGCUUGGUC AUCUAT	122	AUAGAUGACCAAGC UUGGCAAGUUCUU	522	GAACUUGCCA AGCUUGGUC	922
LPA - 328 8	AACUUGCCAAGCUUGGUCA ACUATG	123	CAUAGUUGACCAAG CUUGGCAAGUUCU	523	AACUUGCCAA GCUUGGUCA	923
LPA - 328 9	ACUUGCCAAGCUUGGUCAU AUAUGA	124	UCAUAUAUGACCAA GCUUGGCAAGUUC	524	ACUUGCCAAG CUUGGUCAU	924
LPA - 329 0	CUUGCCAAGCUUGGUCAUC AAUGAC	125	GUCAUUGAUGACCA AGCUUGGCAAGUU	525	CUUGCCAAGC UUGGUCAUC	925
LPA - 329 1	UUGCCAAGCUUGGUCAUCU AUGACA	126	UGUCAUAGAUGACC AAGCUUGGCAAGU	526	UUGCCAAGCU UGGUCAUCU	926
LPA - 329 2	UGCCAAGCUUGGUCAUCUA AGACAC	127	GUGUCUUAGAUGAC CAAGCUUGGCAAG	527	UGCCAAGCUU GGUCAUCUA	927

LPA - 329 8	GCUUGGUCAUCUAUGACAC AACACC	128	GGUGUUGUGUCAUA GAUGACCAAGCUU	528	GCUUGGUCAU CUAUGACAC	928
LPA - 330 0	UUGGUCAUCUAUGACACCA AACCAG	129	CUGGUUUGGUGUCA UAGAUGACCAAGC	529	UUGGUCAUCU AUGACACCA	929
LPA - 330 1	UGGUCAUCUAUGACACCAC ACCAGC	130	GCUGGUGUGGUGUC AUAGAUGACCAAG	530	UGGUCAUCUA UGACACCAC	930
LPA - 330 3	GUCAUCUAUGACACCACAC AAGCAT	131	AUGCUUGUGUGGUG UCAUAGAUGACCA	531	GUCAUCUAUG ACACCACAC	931
LPA - 330 5	CAUCUAUGACACCACACCA ACAUAG	132	CUAUGUUGGUGUGG UGUCAUAGAUGAC	532	CAUCUAUGAC ACCACACCA	932
LPA - 330 6	AUCUAUGACACCACACCAG AAUAGT	133	ACUAUUCUGGUGUG GUGUCAUAGAUGA	533	AUCUAUGACA CCACACCAG	933
LPA - 330 8	CUAUGACACCACACCAGCA AAGUCG	134	CGACUUGCUGGUG UGGUGUCAUAGAU	534	CUAUGACACC ACACCAGCA	934
LPA - 332 9	GUCGGACCCCAGAAAACUA ACCAAA	135	UUUGGUUAGUUUUC UGGGGUCCGACUA	535	GUCGGACCCC AGAAAACUA	935
LPA - 333 0	UCGGACCCCAGAAAACUAC ACAAAT	136	AUUUGUGUAGUUUU CUGGGGUCCGACU	536	UCGGACCCCA GAAAACUAC	936
LPA - 334 0	GAAAACUACCCAAAUGCUG ACCUGA	137	UCAGGUCAGCAUUU GGGUAGUUUUCUG	537	GAAAACUACC CAAAUGCUG	937
LPA - 339 1	GCUGAGAUUCGCCCUGGU AUUACA	138	UGUAAUACCAAGGG CGAAUCUCAGCAU	538	GCUGAGAUUC GCCCUGGU	938
LPA - 339 2	CUGAGAUUCGCCCUGGUG AUACAC	139	GUGUAUCACCAAGG GCGAAUCUCAGCA	539	CUGAGAUUCG CCCUGGUG	939
LPA - 339 4	GAGAUUCGCCCUGGUGUU ACACCA	140	UGGUGUAACACCAA GGGCGAAUCUCAG	540	GAGAUUCGCC CUUGGUGUU	940
LPA - 339 5	AGAUUCGCCCUGGUGUUA AACCAT	141	AUGGUUUAACACCA AGGGCGAAUCUCA	541	AGAUUCGCCC UUGGUGUUA	941
LPA - 339 8	UUCGCCCUGGUGUACAC AAUGGA	142	UCCAUGUGUAACA CCAAGGGCGAAUC	542	UUCGCCCUG GUGUACAC	942

LPA - 340 4	CUUGGUGUUACACCAUGGA ACCCAG	143	CUGGGUCCAUGGU GUAACACCAAGG	543	CUUGGUGUUA CACCAUGGA	943
LPA - 340 5	UUGGUGUUACACCAUGGAU ACCAAT	144	ACUGGUAUCCAUGG UGUAACACCAAGG	544	UUGGUGUUAC ACCAUGGAU	944
LPA - 340 6	UGGUGUUACACCAUGGAUC ACAGTG	145	CACUGUGAUCCAUG GUGUAACACCAAG	545	UGGUGUUACA CCAUGGAUC	945
LPA - 340 7	GGUGUUACACCAUGGAUCC AAGUGT	146	ACACUUGGAUCCA GGUGUAACACCAA	546	GGUGUUACAC CAUGGAUCC	946
LPA - 340 9	UGUUACACCAUGGAUCCCA AUGUCA	147	UGACAUUGGGAUCC AUGGUGUAACACC	547	UGUUACACCA UGGAUCCCA	947
LPA - 347 2	GAAUCAAGUGUCCUUGCAA AUCUCA	148	UGAGAUUUGCAAGG ACACUUGAUUCUG	548	GAAUCAAGUG UCCUUGCAA	948
LPA - 347 3	AAUCAAGUGUCCUUGCAAC ACUCAC	149	GUGAGUGUUGCAAG GACACUUGAUUCU	549	AAUCAAGUGU CCUUGCAAC	949
LPA - 347 4	AUCAAGUGUCCUUGCAACU AUCACG	150	CGUGAUAGUUGCAA GGACACUUGAUUC	550	AUCAAGUGUC CUUGCAACU	950
LPA - 358 4	AUGGACAGAGUUAUCGAGG AUCAT	151	AAUGAUCCUCGAUA ACUCUGUCCAUA	551	AUGGACAGAG UUAUCGAGG	951
LPA - 358 5	UGGACAGAGUUAUCGAGGC ACAUTC	152	GAAUGUGCCUCGAU AACUCUGUCCAUC	552	UGGACAGAGU UAUCGAGGC	952
LPA - 365 5	ACACCACACUGGCAUCAGA AGACAA	153	UUGUCUUCUGAUGC CAGUGUGGUGUCA	553	ACACCACACU GGCAUCAGA	953
LPA - 374 7	UUGGUGUUUAUACCAUGGAU ACCAAT	154	AUUGGUAUCCAUGG UAUAACACCAAGG	554	UUGGUGUUUA ACCAUGGAU	954
LPA - 374 8	UGGUGUUUAUACCAUGGAUC ACAATG	155	CAUUGUGAUCCAUG GUUAACACCAAG	555	UGGUGUUUAU CCAUGGAUC	955
LPA - 374 9	GGUGUUUAUACCAUGGAUCC AAAUGT	156	ACAUUUGGAUCCA GGUUAACACCAA	556	GGUGUUUAUAC CAUGGAUCC	956
LPA - 375 0	GUGUUUAUACCAUGGAUCCC AAUGTC	157	GACAUUGGGAUCCA UGGUUAACACCA	557	GUGUUUAUACC AUGGAUCCC	957

LPA - 377 3	UCAGAUUGGAGUACUGCAA ACUGAC	158	GUCAGUUUGCAGUA CUCCCAUCUGACA	558	UCAGAUUGGGA GUACUGCAA	958
LPA - 377 6	GAUGGGAGUACUGCAACCU AACACA	159	UGUGUUAGGUUGCA GUACUCCCAUCUG	559	GAUGGGAGUA CUGCAACCU	959
LPA - 377 7	AUGGGAGUACUGCAACCU ACACAA	160	UUGUGUCAGGUUGC AGUACUCCCAUCU	560	AUGGGAGUAC UGCAACCU	960
LPA - 377 8	UGGAGUACUGCAACCUGA AACAA	161	AUUGUUUCAGGUUG CAGUACUCCCAUC	561	UGGAGUACU GCAACCUGA	961
LPA - 377 9	GGGAGUACUGCAACCUGAC ACAATG	162	CAUUGUGUCAGGUU GCAGUACUCCCAU	562	GGGAGUACUG CAACCUGAC	962
LPA - 384 0	GGCUGUUUCUGAACAGCA ACAACG	163	CGUUGUUGCUUGUU CAGAAACAGCCGU	563	GGCUGUUUCU GAACAAGCA	963
LPA - 384 4	GUUUCUGAACAGCACCAA AGGAGC	164	GCUCCUUUGGUGCU UGUUCAGAAACAG	564	GUUUCUGAAC AAGCACCAA	964
LPA - 392 7	CUCCACCACUGUACAGGA AGGACA	165	UGUCCUCCUGUAA CAGUGGUGGAGAA	565	CUCCACCACU GUUACAGGA	965
LPA - 392 8	UCCACCACUGUACAGGAA AGACAT	166	AUGUCUUCCUGUA ACAGUGGUGGAGA	566	UCCACCACUG UUACAGGAA	966
LPA - 392 9	CCACCACUGUACAGGAAG AACATG	167	CAUGUUCUCCUGU AACAGUGGUGGAG	567	CCACCACUGU UACAGGAAG	967
LPA - 397 2	GACACCACACUGGCAUCAG AGAACC	168	GGUUCUCUGAUGCC AGUGUGGUGUCAU	568	GACACCACAC UGGCAUCAG	968
LPA - 397 3	ACACCACACUGGCAUCAGA AAACCA	169	UGGUUUUCUGAUGC CAGUGUGGUGUCA	569	ACACCACACU GGCAUCAGA	969
LPA - 399 9	AGAAUACUACCCAAAUGGU AGCCTG	170	CAGGCUACCAUUUG GGUAGUAUUCUGU	570	AGAAUACUAC CCAAAUGGU	970
LPA - 400 0	GAAUACUACCCAAAUGGUG ACCUGA	171	UCAGGUCACCAUUU GGGUAGUAUUCUG	571	GAAUACUACC CAAAUGGUG	971
LPA - 400 1	AAUACUACCCAAAUGGUG ACUGAC	172	GUCAGUCCACCAUU UGGGUAGUAUUCU	572	AAUACUACCC AAAUGGUGG	972

LPA - 418 5	UCCUUCUGAAGAAGCACCA ACUGAA	173	UUCAGUUGGUGCUU CUUCAGAAGGAAG	573	UCCUUCUGAA GAAGCACCA	973
LPA - 418 6	CCUUCUGAAGAAGCACCAA AUGAAA	174	UUUCAUUUGGUGCU UCUUCAGAAGGAA	574	CCUUCUGAAG AAGCACCAA	974
LPA - 418 7	CUUCUGAAGAAGCACCAAC AGAAAA	175	UUUUCUGUUGGUGC UUCUUCAGAAGGA	575	CUUCUGAAGA AGCACCAAC	975
LPA - 418 8	UUCUGAAGAAGCACCAACU AAAAAC	176	GUUUUUAGUUGGUG CUUCUUCAGAAGG	576	UUCUGAAGAA GCACCAACU	976
LPA - 418 9	UCUGAAGAAGCACCAACUG AAAACA	177	UGUUUUCAGUUGGU GCUUCUUCAGAAG	577	UCUGAAGAAG CACCAACUG	977
LPA - 419 0	CUGAAGAAGCACCAACUGA AAACAG	178	CUGUUUUCAGUUGG UGCUUCUUCAGAA	578	CUGAAGAAGC ACCAACUGA	978
LPA - 419 1	UGAAGAAGCACCAACUGAA AACAGC	179	GCUGUUUUCAGUUG GUGCUUCUUCAGA	579	UGAAGAAGCA CCAACUGAA	979
LPA - 419 2	GAAGAAGCACCAACUGAAA ACAGCA	180	UGCUGUUUUCAGUU GGUGCUUCUUCAG	580	GAAGAAGCAC CAACUGAAA	980
LPA - 419 3	AAGAAGCACCAACUGAAAA AAGCAC	181	GUGCUUUUUCAGU UGGUGCUUCUUC	581	AAGAAGCAC AACUGAAAA	981
LPA - 419 4	AGAAGCACCAACUGAAAAC AGCACT	182	AGUGCUGUUUUCAG UUGGUGCUUCUUC	582	AGAAGCACCA ACUGAAAAC	982
LPA - 419 5	GAAGCACCAACUGAAAACA ACACTG	183	CAGUGUUGUUUUC GUUGGUGCUUCUUC	583	GAAGCACCAA CUGAAAACA	983
LPA - 419 6	AAGCACCAACUGAAAACAG AACUGG	184	CCAGUUCUGUUUUC AGUUGGUGCUUCU	584	AAGCACCAAC UGAAAACAG	984
LPA - 423 9	AGGUGAUGGACAGAGUUAU AGAGGC	185	GCCUCUAUAACUCU GUCCAUCACCUUG	585	AGGUGAUGGA CAGAGUUAU	985
LPA - 426 9	CUCCACCACUAUCACAGGA AGAACA	186	UGUUCUUCUGUGA UAGUGGUGGAGAG	586	CUCCACCACU AUCACAGGA	986
LPA - 427 0	UCCACCACUAUCACAGGAA AAACAT	187	AUGUUUUUCCUGUG AUAGUGGUGGAGA	587	UCCACCACUA UCACAGGAA	987

LPA - 427 1	CCACCACUACAGGAAG AACATG	188	CAUGUUCUCCUGU GAUAGUGGUGGAG	588	CCACCACUAC CAGGAAG	988
LPA - 427 2	CACCACUACAGGAAGA ACAUGT	189	ACAUGUUCUCCUG UGAUAGUGGUGGA	589	CACCACUAC ACAGGAAGA	989
LPA - 427 3	ACCACUACAGGAAGAA AAUGTC	190	GACAUUUUCUCCU GUGAUAGUGGUGG	590	ACCACUAC CAGGAAGAA	990
LPA - 427 4	CCACUACAGGAAGAAC AUGUCA	191	UGACAUUUCUCC UGUGAUAGUGGUG	591	CCACUAC AGGAAGAAC	991
LPA - 427 5	CACUACAGGAAGAAC AGUCAG	192	CUGACUUGUUCUCC CUGUGAUAGUGGU	592	CACUAC GGAAGAAC	992
LPA - 427 6	ACUACAGGAAGAACAU AUCAGT	193	ACUGAUUGUUCU CCUGUGAUAGUGG	593	ACUACAG GAAGAACAU	993
LPA - 427 7	CUACAGGAAGAACAU ACAGTC	194	GACUGUCAUGUUC UCCUGUGAUAGUG	594	CUACAGG AAGAACAU	994
LPA - 427 8	UAUCAGGAAGAACAU AAGUCT	195	AGACUACAUUGUCC UCCUGUGAUAGU	595	UAUCAGG AGAACAU	995
LPA - 427 9	AUCAGGAAGAACAU AGUCTT	196	AAGACUGACAUUU CUUCCUGUGAUAG	596	AUCAGGA GAACAU	996
LPA - 428 0	UCACAGGAAGAACAU AUCUTG	197	CAAGAUUGACAU UCUCCUGUGAU	597	UCACAGG AACAU	997
LPA - 428 1	CACAGGAAGAACAU ACUUGG	198	CCAAGUCUGACAU UUCUCCUGUGAU	598	CACAGGA ACAUG	998
LPA - 428 2	ACAGGAAGAACAU AUUGGT	199	ACCAAUACUGACAU GUUCUCCUGUGA	599	ACAGGA CAUG	999
LPA - 428 5	GGAAGAACAU AGUCGT	200	ACGACUAAGACUGA CAUGUUCUCCUG	600	GGAAGAACAU GUCAGUCUU	1000
LPA - 428 6	GAAGAACAU AUCGTC	201	GACGAUCAAGACUG ACAUGUUCUCCU	601	GAAGAACAU UCAGUCUUG	1001
LPA - 428 7	AAGAACAUGUCAGUCUUG ACGUCT	202	AGACGUCCAAGACU GACAUGUUCUCC	602	AAGAACAUGU CAGUCUUGG	1002

LPA - 428 8	AGAACAUGUCAGUCUUGGU AGUCTA	203	UAGACUACCAAGAC UGACAUGUUCUUC	603	AGAACAUGUC AGUCUUGGU	1003
LPA - 432 5	GGCAUCGGAGGAUCCCAUU AUACTA	204	UAGUAUAAUGGGAU CCUCCGAUGCCAA	604	GGCAUCGGAG GAUCCCAUU	1004
LPA - 434 6	ACUAUCCAAAUGCUGGCCU AACCAG	205	CUGGUUAGGCCAGC AUUUGGAUAGUAU	605	ACUAUCCAAA UGCUGGCCU	1005
LPA - 451 7	GCACAGAGGCUCUUCUGA ACAAGC	206	GCUUGUUCAGAAGG AGCCUCUGUGCUU	606	GCACAGAGGC UCCUUCUGA	1006
LPA - 452 7	UCCUUCUGAACACGACCA ACUGAG	207	CUCAGUUGGUGCUU GUUCAGAAGGAGC	607	UCCUUCUGAA CAAGCACCA	1007
LPA - 452 8	CCUUCUGAACAGCACCAC AUGAGA	208	UCUCAUGUGGUGCU UGUUCAGAAGGAG	608	CCUUCUGAAC AAGCACCAC	1008
LPA - 452 9	CUUCUGAACAGCACCACC AGAGAA	209	UUCUCUGGUGGUGC UUGUUCAGAAGGA	609	CUUCUGAACAC AGCACCACC	1009
LPA - 453 0	UUCUGAACAGCACCACCU AAGAAA	210	UUUCUUAGGUGGUG CUUGUUCAGAAGG	610	UUCUGAACAA GCACCACCU	1010
LPA - 453 1	UCUGAACAGCACCACCUG AGAAAA	211	UUUUUCAGGUGGU GCUUGUUCAGAAG	611	UCUGAACAG CACCACCUG	1011
LPA - 453 2	CUGAACAGCACCACCUGA AAAAAG	212	CUUUUUUCAGGUGG UGCUUGUUCAGAA	612	CUGAACAGC ACCACCUGA	1012
LPA - 453 3	UGAACAGCACCACCUGAG AAAAGC	213	GCUUUUCUCAGGUG GUGCUUGUUCAGA	613	UGAACAGCA CCACCUGAG	1013
LPA - 453 4	GAACAAGCACCACCUGAGA AAAGCC	214	GGCUUUUCAGGU GGUGCUUGUUCAG	614	GAACAAGCAC CACCUGAGA	1014
LPA - 453 5	AACAAGCACCACCUGAGAA AAGCCC	215	GGGCUUUUCAGG UGGUGCUUGUUC	615	AACAAGCACC ACCUGAGAA	1015
LPA - 453 7	CAAGCACCACCUGAGAAAA ACCTTG	216	CAGGGUUUUUCUCA GGUGGUGCUUGUU	616	CAAGCACCAC CUGAGAAAA	1016
LPA - 453 8	AAGCACCACCUGAGAAAAG ACCUGT	217	ACAGGUCUUUUCUC AGGUGGUGCUUGU	617	AAGCACCACC UGAGAAAAG	1017

LPA - 453 9	AGCACCACCUGAGAAAAGC ACUGTG	218	CACAGUGCUIUUCU CAGGUGGUGCUUG	618	AGCACCACCU GAGAAAAGC	1018
LPA - 454 7	CUGAGAAAAGCCUGUGGU ACAGGA	219	UCCUGUACCACAGG GCUUUUCUCAGGU	619	CUGAGAAAAG CCCUGUGGU	1019
LPA - 455 6	GCCCUGUGGUCCAGGAUUG AUACCA	220	UGGUAUCAAUCCUG GACCACAGGGCUU	620	GCCCUGUGGU CCAGGAUUG	1020
LPA - 455 9	CUGUGGUCCAGGAUUGCUA ACAUGG	221	CCAUGUUAGCAAUC CUGGACCACAGGG	621	CUGUGGUCCA GGAUUGCUA	1021
LPA - 461 1	CUCCACCACUGUCACAGGA AGGACC	222	GGUCCUCCUGUGA CAGUGGUGGAGGA	622	CUCCACCACU GUCACAGGA	1022
LPA - 461 2	UCCACCACUGUCACAGGAA AGACCT	223	AGGUCUUCCUGUG ACAGUGGUGGAGG	623	UCCACCACUG UCACAGGAA	1023
LPA - 464 2	UCUUGGUCAUCUAUGAUAC AACACT	224	AGUGUUGUAUCAUA GAUGACCAAGAUU	624	UCUUGGUCAU CUAUGAUAC	1024
LPA - 464 3	CUUGGUCAUCUAUGAUACC ACACTG	225	CAGUGUGGUUAUCAU AGAUGACCAAGAU	625	CUUGGUCAUC UAUGAUACC	1025
LPA - 464 4	UUGGUCAUCUAUGAUACCA AACUGG	226	CCAGUUUGGUUAUCA UAGAUGACCAAGA	626	UUGGUCAUCU AUGAUACCA	1026
LPA - 464 5	UGGUCAUCUAUGAUACCAC ACUGGC	227	GCCAGUGUGGUUAUC AUAGAUGACCAAG	627	UGGUCAUCUA UGAUACCAC	1027
LPA - 464 6	GGUCAUCUAUGAUACCACA AUGGCA	228	UGCCAUIUGUGGUUAU CAUAGAUGACCAA	628	GGUCAUCUAU GAUACCACA	1028
LPA - 464 7	GUCAUCUAUGAUACCACAC AGGCAT	229	AUGCCUGUGUGGUUA UCAUAGAUGACCA	629	GUCAUCUAUG AUACCACAC	1029
LPA - 464 8	UCAUCUAUGAUACCACACU AGCATC	230	GAUGCUAGUGUGGU AUCAUAGAUGACC	630	UCAUCUAUGA UACCACACU	1030
LPA - 464 9	CAUCUAUGAUACCACACUG ACAUCA	231	UGAUGUCAGUGUGG UAUCAUAGAUGAC	631	CAUCUAUGAU ACCACACUG	1031
LPA - 465 0	AUCUAUGAUACCACACUGG AAUCAG	232	CUGAUUCCAGUGUG GUAUCAUAGAUGA	632	AUCUAUGAUA CCACACUGG	1032

LPA - 465 1	UCUAUGAUACCACACUGGC AUCAGA	233	UCUGAUGCCAGUGU GGUAUCAUAGAUG	633	UCUAUGAUAC CACACUGGC	1033
LPA - 465 2	CUAUGAUACCACACUGGCA ACAGAG	234	CUCUGUUGCCAGUG UGGUAUCAUAGAU	634	CUAUGAUACC ACACUGGCA	1034
LPA - 465 5	UGAUACCACACUGGCAUCA AAGGAC	235	GUCCUUUGAUGCCA GUGUGGUAUCAUA	635	UGAUACCACA CUGGCAUCA	1035
LPA - 465 7	AUACCACACUGGCAUCAGA AGACCC	236	GGGCUUCUGAUGC CAGUGUGGUAUCA	636	AUACCACACU GGCAUCAGA	1036
LPA - 467 3	AGAGGACCCCAGAAAACUA ACCAAA	237	UUUGGUUAGUUUUC UGGGGUCCUCUGA	637	AGAGGACCCC AGAAAACUA	1037
LPA - 467 4	GAGGACCCCAGAAAACUAC ACAAAT	238	AUUUGUGUAGUUUU CUGGGGUCCUCUG	638	GAGGACCCCA GAAAACUAC	1038
LPA - 471 2	AGAACUACUGCAGGAAUCC AGAUTC	239	GAAUCUGGAUCCU GCAGUAGUUCUG	639	AGAACUACUG CAGGAAUCC	1039
LPA - 471 5	ACUACUGCAGGAAUCCAGA AUCUGG	240	CCAGAUUCUGGAUU CCUGCAGUAGUUC	640	ACUACUGCAG GAAUCCAGA	1040
LPA - 471 7	UACUGCAGGAAUCCAGAUU AUGGGA	241	UCCCAUAAUCUGGA UUCUGCAGUAGU	641	UACUGCAGGA AUCCAGAUU	1041
LPA - 471 8	ACUGCAGGAAUCCAGAUUC AGGGAA	242	UUCCUGAAUCUGG AUUCCUGCAGUAG	642	ACUGCAGGAA UCCAGAUUC	1042
LPA - 471 9	CUGCAGGAAUCCAGAUUCU AGGAAA	243	UUUCCUAGAAUCUG GAUUCUGCAGUA	643	CUGCAGGAAU CCAGAUUCU	1043
LPA - 472 0	UGCAGGAAUCCAGAUUCUG AGAAAC	244	GUUUCUCAGAAUCU GGAUUCUGCAGU	644	UGCAGGAAUC CAGAUUCUG	1044
LPA - 472 1	GCAGGAAUCCAGAUUCUGG AAAACA	245	UGUUUUCAGAAUC UGGAUUCUGCAG	645	GCAGGAAUCC AGAUUCUGG	1045
LPA - 472 4	GGAAUCCAGAUUCUGGGAA ACAACC	246	GGUUGUUUCCAGAA AUCUGGAUUCUG	646	GGAAUCCAGAA UUCUGGGAA	1046
LPA - 473 8	GGGAAACAACCCUGGUGUU ACACAA	247	UUGUGUAAACACCAG GGUUGUUUCCAG	647	GGGAAACAAC CCUGGUGUU	1047

LPA - 473 9	GGAAACAACCCUGGUGUUA ACAAC	248	GUUGUUUACACCA GGGUGUUUCCCA	648	GGAAACAACC CUGGUGUUA	1048
LPA - 477 1	UGUGUGAGGUGGGAGUACU ACAATC	249	GAUUGUAGUACUCC CACCUCACACACG	649	UGUGUGAGGU GGGAGUACU	1049
LPA - 477 2	GUGUGAGGUGGGAGUACUG AAAUCT	250	AGAUUUCAGUACUC CCACCUCACACAC	650	GUGUGAGGUG GGAGUACUG	1050
LPA - 477 4	GUGAGGUGGGAGUACUGCA AUCUGA	251	UCAGAUUGCAGUAC UCCCACCUCACAC	651	GUGAGGUGGG AGUACUGCA	1051
LPA - 477 5	UGAGGUGGGAGUACUGCAA ACUGAC	252	GUCAGUUUGCAGUA CUCCCACCUCACA	652	UGAGGUGGGGA GUACUGCAA	1052
LPA - 479 5	CUGACACAAUGCUCAGAAA AAGAACT	253	AUUCUUUUUCUGAG CAUUGUGUCAGAU	653	CUGACACAAU GCUCAGAAA	1053
LPA - 479 6	UGACACAAUGCUCAGAAAC AGAATC	254	GAUUCUGUUUCUGA GCAUUGUGUCAGA	654	UGACACAAUG CUCAGAAAC	1054
LPA - 479 7	GACACAAUGCUCAGAAACA AAAUCA	255	UGAUUUUGUUUCUG AGCAUUGUGUCAG	655	GACACAAUGC UCAGAAACA	1055
LPA - 479 8	ACACAAUGCUCAGAAACAG AAUCAG	256	CUGAUUCUGUUUCU GAGCAUUGUGUCA	656	ACACAAUGCU CAGAAACAG	1056
LPA - 479 9	CACAAUGCUCAGAAACAGA AUCAGG	257	CCUGAUUCUGUUUC UGAGCAUUGUGUC	657	CACAAUGCUC AGAAACAGA	1057
LPA - 480 0	ACAAUGCUCAGAAACAGAA ACAGGT	258	ACCUGUUUCUGUUU CUGAGCAUUGUGU	658	ACAAUGCUC GAAACAGAA	1058
LPA - 480 1	CAAUGCUCAGAAACAGAAU AAGGTG	259	CACCUUAUUCUGUU UCUGAGCAUUGUG	659	CAAUGCUCAG AAACAGAAU	1059
LPA - 480 2	AAUGCUCAGAAACAGAAUC AGGUGT	260	ACACCUGAUUCUGU UUCUGAGCAUUGU	660	AAUGCUCAGA AACAGAAUC	1060
LPA - 480 3	AUGCUCAGAAACAGAAUCA AGUGTC	261	GACACUUGAUUCUG UUUCUGAGCAUUG	661	AUGCUCAGAA ACAGAAUCA	1061
LPA - 480 4	UGCUCAGAAACAGAAUCAG AUGUCC	262	GGACAUCUGAUUCU GUUUCUGAGCAUU	662	UGCUCAGAAA CAGAAUCAG	1062

LPA - 480 6	CUCAGAAACAGAAUCAGGU AUCCTA	263	UAGGAUACCUGAUU CUGUUUCUGAGCA	663	CUCAGAAACA GAAUCAGGU	1063
LPA - 480 8	CAGAAACAGAAUCAGGUGU ACUAGA	264	UCUAGUACACCUGA UUCUGUUUCUGAG	664	CAGAAACAGA AUCAGGUGU	1064
LPA - 480 9	AGAAACAGAAUCAGGUGUC AUAGAG	265	CUCUAGACACCUG AUUCUGUUUCUGA	665	AGAAACAGAA UCAGGUGUC	1065
LPA - 481 0	GAAACAGAAUCAGGUGUCC AAGAGA	266	UCUCUUGGACACCU GAUUCUGUUUCUG	666	GAAACAGAAU CAGGUGUCC	1066
LPA - 481 1	AAACAGAAUCAGGUGUCCU AGAGAC	267	GUCUCUAGGACACC UGAUUCUGUUUCU	667	AAACAGAAUC AGGUGUCCU	1067
LPA - 481 2	AACAGAAUCAGGUGUCCUA AAGACT	268	AGUCUUUAGGACAC CUGAUUCUGUUUC	668	AACAGAAUCA GGUGUCCUA	1068
LPA - 481 4	CAGAAUCAGGUGUCCUAGA AACUCC	269	GGAGUUUCUAGGAC ACCUGAUUCUGUU	669	CAGAAUCAGG UGUCCUAGA	1069
LPA - 481 6	GAAUCAGGUGUCCUAGAGA AUCCCA	270	UGGGAUUCUCUAGG ACACCUGAUUCUG	670	GAAUCAGGUG UCCUAGAGA	1070
LPA - 481 8	AUCAGGUGUCCUAGAGACU ACCACT	271	AGUGGUAGUCUCUA GGACACCUGAUUC	671	AUCAGGUGUC CUAGAGACU	1071
LPA - 482 2	GGUGUCCUAGAGACUCCCA AUGUTG	272	CAACAUUGGGAGUC UCUAGGACACCUG	672	GGUGUCCUAG AGACUCCCA	1072
LPA - 482 7	CCUAGAGACUCCACUGUU AUUCCA	273	UGGAAUAACAGUGG GAGUCUCUAGGAC	673	CCUAGAGACU CCCACUGUU	1073
LPA - 482 8	CUAGAGACUCCACUGUUG AUCCAG	274	CUGGAUCAACAGUG GGAGUCUCUAGGA	674	CUAGAGACUC CCACUGUUG	1074
LPA - 482 9	UAGAGACUCCACUGUUGU ACCACT	275	ACUGGUACAACAGU GGGAGUCUCUAGG	675	UAGAGACUCC CACUGUUGU	1075
LPA - 483 0	AGAGACUCCACUGUUGUU ACAGTT	276	AACUGUAACAACAG UGGGAGUCUCUAG	676	AGAGACUCC ACUGUUGUU	1076
LPA - 483 1	GAGACUCCACUGUUGUUC AAGUTC	277	GAACUUGAACAACA GUGGGAGUCUCUA	677	GAGACUCCCA CUGUUGUUC	1077

LPA - 483 2	AGACUCCACUGUUGUUC AGUUC	278	GGAACUGGAACAAC AGUGGAGUCUCU	678	AGACUCCAC UGUUGUUC	1078
LPA - 486 7	GCUCAUUCUGAAGCAGCAC AACTG	279	CAGUUGUGUGUCU UCAGAAUGAGCCU	679	GCUCAUUCUG AAGCAGCAC	1079
LPA - 486 8	CUCAUUCUGAAGCAGCAC AACUGA	280	UCAGUUGGUGUGC UUCAGAAUGAGCC	680	CUCAUUCUGA AGCAGCAC	1080
LPA - 486 9	UCAUUCUGAAGCAGCACCA ACUGAG	281	CUCAGUUGGUGUGC CUUCAGAAUGAGC	681	UCAUUCUGAA GCAGCACCA	1081
LPA - 487 0	CAUUCUGAAGCAGCACCAA AUGAGC	282	GCUCAUUGGUGUCU GCUUCAGAAUGAG	682	CAUUCUGAAG CAGCACCAA	1082
LPA - 487 1	AUUCUGAAGCAGCACCAAC AGAGCA	283	UGCUCUGUUGGUGC UGCUCAGAAUGA	683	AUUCUGAAGC AGCACCAAC	1083
LPA - 487 2	UUCUGAAGCAGCACCAACU AAGCAA	284	UUGCUUAGUUGGUG CUGCUUCAGAAUG	684	UUCUGAAGCA GCACCAACU	1084
LPA - 487 3	UCUGAAGCAGCACCAACUG AGCAAA	285	UUUGCUCAGUUGGU GUCGUUCAGAAU	685	UCUGAAGCAG CACCAACUG	1085
LPA - 487 4	CUGAAGCAGCACCAACUGA ACAAAC	286	GUUUGUUCAGUUGG UGCUCUUCAGAA	686	CUGAAGCAGC ACCAACUGA	1086
LPA - 487 5	UGAAGCAGCACCAACUGAG AAAACC	287	GGUUUUCUAGUUG GUGCUGCUUCAGA	687	UGAAGCAGCA CCAACUGAG	1087
LPA - 487 6	GAAGCAGCACCAACUGAGC AAACCC	288	GGGUUUGCUCAGUU GGUGCUGCUUCAG	688	GAAGCAGCAC CAACUGAGC	1088
LPA - 487 7	AAGCAGCACCAACUGAGCA AACCCC	289	GGGUUUGCUCAGU UGGUGCUGCUUCA	689	AAGCAGCAC AACUGAGCA	1089
LPA - 491 2	CAGUGCUACCAUGGUAAUG ACCAGA	290	UCUGGUCAUUACCA UGGUAGCACUGCC	690	CAGUGCUACC AUGGUAAUG	1090
LPA - 491 3	AGUGCUACCAUGGUAAUGG ACAGAG	291	CUCUGUCCAUUACC AUGGUAGCACUGC	691	AGUGCUACCA UGGUAAUGG	1091
LPA - 494 8	ACAUUCUCCACCACUGUCA AAGGAA	292	UUCUUCUGACAGUG GUGGAGAAUGUGC	692	ACAUUCUCCA CCACUGUCA	1092

LPA - 495 9	CACUGUCACAGGAAGGACA AGUCAA	293	UUGACUUGUCCUUC CUGUGACAGUGGU	693	CACUGUCACA GGAAGGACA	1093
LPA - 496 0	ACUGUCACAGGAAGGACAU AUAAT	294	AUUGAUUGUCCUUC CCUGUGACAGUGG	694	ACUGUCACAG GAAGGACAU	1094
LPA - 496 1	CUGUCACAGGAAGGACAUG ACAATC	295	GAUUGUCAUGUCCU UCCUGUGACAGUG	695	CUGUCACAGG AAGGACAUG	1095
LPA - 496 2	UGUCACAGGAAGGACAUGU AAAUCT	296	AGAUUACAUGUCC UCCUGUGACAGU	696	UGUCACAGGA AGGACAUGU	1096
LPA - 496 3	GUCACAGGAAGGACAUGUC AAUCTT	297	AAGAUGACAUGUC CUCCUGUGACAG	697	GUCACAGGAA GGACAUGUC	1097
LPA - 496 4	UCACAGGAAGGACAUGUCA AUCUTG	298	CAAGAUUGACAUGU CCUCCUGUGACA	698	UCACAGGAAG GACAUGUCA	1098
LPA - 496 6	ACAGGAAGGACAUGUCAAU AUUGGT	299	ACCAAUAUUGACAU GUCCUCCUGUGA	699	ACAGGAAGGA CAUGUCAAU	1099
LPA - 496 7	CAGGAAGGACAUGUCAAUUC AUGGTC	300	GACCAUGAUUGACA UGUCCUCCUGUG	700	CAGGAAGGAC AUGUCAAUUC	1100
LPA - 496 8	AGGAAGGACAUGUCAAUUCU AGGUCA	301	UGACCUAGAUUGAC AUGUCCUCCUGU	701	AGGAAGGACA UGUCAAUUCU	1101
LPA - 496 9	GGAAGGACAUGUCAAUUCUU AGUCAT	302	AUGACUAAGAUUGA CAUGUCCUCCUG	702	GGAAGGACA GUCAAUUCUU	1102
LPA - 497 0	GAAGGACAUGUCAAUUCUUG AUCATC	303	GAUGAUCAAGAUUG ACAUGUCCUCCU	703	GAAGGACAUG UCAAUUCUUG	1103
LPA - 497 1	AAGGACAUGUCAAUUCUUGG ACAUCC	304	GGAUGUCCAAGAUU GACAUGUCCUCC	704	AAGGACAUGU CAAUCUUGG	1104
LPA - 497 2	AGGACAUGUCAAUUCUUGGU AAUCCA	305	UGGAUUACCAAGAU UGACAUGUCCUUC	705	AGGACAUGUC AAUCUUGGU	1105
LPA - 497 3	GGACAUGUCAAUUCUUGGUC AUCCAT	306	AUGGAUGACCAAGA UUGACAUGUCCUU	706	GGACAUGUCA AUCUUGGUC	1106
LPA - 497 4	GACAUGUCAAUUCUUGGUCA ACCATG	307	CAUGGUUGACCAAG AUUGACAUGUCCU	707	GACAUGUCA UCUUGGUCA	1107

LPA - 497 5	ACAUGUCAAUCUUGGUCAU ACAUGA	308	UCAUGUAUGACCAA GAUUGACAUGUCC	708	ACAUGUCAAU CUUGGUCAU	1108
LPA - 497 6	CAUGUCAAUCUUGGUCAUC AAUGAC	309	GUCAUUGAUGACCA AGAUGACAUGUC	709	CAUGUCAAUC UUGGUCAUC	1109
LPA - 497 7	AUGUCAAUCUUGGUCAUCC AUGACA	310	UGUCAUGGAUGACC AAGAUUGACAUGU	710	AUGUCAAUCU UGGUCAUCC	1110
LPA - 497 8	UGUCAAUCUUGGUCAUCCA AGACAC	311	GUGUCUUGGAUGAC CAAGAUUGACAUG	711	UGUCAAUCUU GGUCAUCCA	1111
LPA - 497 9	GUCAAUCUUGGUCAUCCA AACACC	312	GGUGUUAUGGAUGA CCAAGAUUGACAU	712	GUCAAUCUUG GUCAUCCA	1112
LPA - 498 0	UCAAUCUUGGUCAUCCAUG ACACCA	313	UGGUGUCAUGGAUG ACCAAGAUUGACA	713	UCAAUCUUGG UCAUCCAUG	1113
LPA - 498 1	CAAUCUUGGUCAUCCAUGA AACCAC	314	GUGGUUUAUGGAU GACCAAGAUUGAC	714	CAAUCUUGGU CAUCCAUGA	1114
LPA - 498 2	AAUCUUGGUCAUCCAUGAC ACCACA	315	UGUGGUGUCAUGGA UGACCAAGAUUGA	715	AAUCUUGGUC AUCCAUGAC	1115
LPA - 498 3	AUCUUGGUCAUCCAUGACA ACACAC	316	GUGUGUUGUCAUGG AUGACCAAGAUUG	716	AUCUUGGUCA UCCAUGACA	1116
LPA - 504 8	UGACAAUGAACUACUGCAG AAAUCC	317	GGAUUUCUGCAGUA GUUCAUUGUCAGG	717	UGACAAUGAA CUACUGCAG	1117
LPA - 504 9	GACAAUGAACUACUGCAGG AAUCCA	318	UGGAUUCUGCAGU AGUUCAUUGUCAG	718	GACAAUGAAC UACUGCAGG	1118
LPA - 505 0	ACAAUGAACUACUGCAGGA AUCCAG	319	CUGGAUUCUGCAG UAGUUCAUUGUCA	719	ACAAUGAACU ACUGCAGGA	1119
LPA - 505 1	CAAUGAACUACUGCAGGAA ACCAGA	320	UCUGGUUUCUGCA GUAGUUCAUUGUC	720	CAAUGAACUA CUGCAGGAA	1120
LPA - 505 2	AAUGAACUACUGCAGGAU ACAGAT	321	AUCUGUAUUCUGC AGUAGUUCAUUGU	721	AAUGAACUAC UGCAGGAU	1121
LPA - 505 3	AUGAACUACUGCAGGAUC AAGATG	322	CAUCUUGAUUCCUG CAGUAGUUCAUUG	722	AUGAACUACU GCAGGAUC	1122

LPA - 505 4	UGAACUACUGCAGGAAUCC AGAUGC	323	GCAUCUGGAUCCU GCAGUAGUUAUU	723	UGAACUACUG CAGGAAUCC	1123
LPA - 505 8	CUACUGCAGGAAUCCAGAU ACCGAT	324	AUCGGUAUCUGGAU UCCUGCAGUAGUU	724	CUACUGCAGG AAUCCAGAU	1124
LPA - 508 4	CAGGCCCUUGGUGUUUAC AAUGGA	325	UCCAUGUAAAACA CCAAGGCCUGUA	725	CAGGCCCUUG GUGUUUAC	1125
LPA - 509 0	CUUGGUGUUUACCAUGGA ACCCAG	326	CUGGGUCCAUGGU AAAACACCAAGGG	726	CUUGGUGUUU UACCAUGGA	1126
LPA - 509 1	UUGGUGUUUACCAUGGAC ACCAGC	327	GCUGGUGCCAUGG UAAAACACCAAGG	727	UUGGUGUUU ACCAUGGAC	1127
LPA - 509 2	UGGUGUUUACCAUGGACC ACAGCA	328	UGCUGUGGUCCAUG GUAAAACACCAAG	728	UGGUGUUUUA CCAUGGACC	1128
LPA - 509 3	GGUGUUUACCAUGGACCC AAGCAT	329	AUGCUUGGGUCCA GGUAAAACACCAA	729	GGUGUUUAC CAUGGACCC	1129
LPA - 509 4	GUGUUUACCAUGGACCCC AGCATC	330	GAUCUGGGGUCCA UGGUAAAACACCA	730	GUGUUUACCC AUGGACCCC	1130
LPA - 509 6	GUUUUACCAUGGACCCCAG AAUCAG	331	CUGAUUCUGGGGUC CAUGGUAAAACAC	731	GUUUUACCAU GGACCCCAG	1131
LPA - 512 4	GGAGUACUGCAACCUGACG AGAUGC	332	GCAUCUCGUCAGGU UGCAGUACUCCA	732	GGAGUACUGC AACCUGACG	1132
LPA - 512 5	GAGUACUGCAACCUGACGC AAUGCT	333	AGCAUUGCGUCAGG UUGCAGUACUCCC	733	GAGUACUGCA ACCUGACGC	1133
LPA - 512 7	GUACUGCAACCUGACGCGA AGCUCA	334	UGAGCUUCGCGUCA GGUUGCAGUACUC	734	GUACUGCAAC CUGACGCGA	1134
LPA - 512 8	UACUGCAACCUGACGCGAU ACUCAG	335	CUGAGUAUCGCGUC AGGUUGCAGUACU	735	UACUGCAACC UGACGCGAU	1135
LPA - 513 1	UGCAACCUGACGCGAUGCU AAGACA	336	UGUCUAGCAUCGC GUCAGGUUGCAGU	736	UGCAACCUGA CGCGAUGCU	1136
LPA - 513 6	CCUGACGCGAUGCUCAGAC ACAGAA	337	UUCUGUGUCUGAGC AUCGCGUCAGGUU	737	CCUGACGCGA UGCUCAGAC	1137

LPA - 513 7	CUGACGCGAUGCUCAGACA AAGAAG	338	CUUCUUUGUCUGAG CAUCGCGUCAGGU	738	CUGACGCGAU GCUCAGACA	1138
LPA - 514 4	GAUGCUCAGACACAGAAGG AACUGT	339	ACAGUCCUUCUGU GUCUGAGCAUCGC	739	GAUGCUCAGA CACAGAAGG	1139
LPA - 514 5	AUGCUCAGACACAGAAGGG ACUGTG	340	CACAGUCCUUCUG UGUCUGAGCAUCG	740	AUGCUCAGAC ACAGAAGGG	1140
LPA - 515 1	AGACACAGAAGGGACUGUG AUCGCT	341	AGCGAUCACAGUCC CUUCUGUGUCUGA	741	AGACACAGAA GGGACUGUG	1141
LPA - 546 7	GCAUCCUCUUCAUUUGAUU AUGGGA	342	UCCCAUAAUCAAU GAAGAGGAUGCAC	742	GCAUCCUCUU CAUUUGAUU	1142
LPA - 546 8	CAUCCUCUUCAUUUGAUUG AGGGAA	343	UUCCCUCAAUCAA UGAAGAGGAUGCA	743	CAUCCUCUUC AUUUGAUUG	1143
LPA - 546 9	AUCCUCUUCAUUUGAUUGU AGGAAG	344	CUUCCUACAAUCAA AUGAAGAGGAUGC	744	AUCCUCUUC UUUGAUUGU	1144
LPA - 547 0	UCCUCUUCAUUUGAUUGUG AGAAGC	345	GCUUCUCACAAUCA AAUGAAGAGGAUG	745	UCCUCUUCAU UUGAUUGUG	1145
LPA - 547 1	CCUCUUCAUUUGAUUGUGG AAAGCC	346	GGCUUCCACAAUC AAUGAAGAGGAU	746	CCUCUUCAUU UGAUUGUGG	1146
LPA - 547 4	CUUCAUUUGAUUGUGGGAA ACCUCA	347	UGAGGUUCCACACA AUCAAAUGAAGAG	747	CUUCAUUUGA UUGUGGGAA	1147
LPA - 547 5	UUCAUUUGAUUGUGGGAAG ACUCAA	348	UUGAGUCUCCAC AAUCAAUGAAGA	748	UUCAUUUGAU UGUGGGAAG	1148
LPA - 547 6	UCAUUUGAUUGUGGGAAGC AUCAAG	349	CUUGAUGCUCUCCA CAAUCAAUGAAG	749	UCAUUUGAUU GUGGGAAGC	1149
LPA - 547 7	CAUUUGAUUGUGGGAAGCC ACAAGT	350	ACUUGUGGCUUCCC ACAAUCAAUGAA	750	CAUUUGAUUG UGGGAAGCC	1150
LPA - 547 8	AUUUGAUUGUGGGAAGCCU AAAGTG	351	CACUUUAGGCUUCC CACAAUCAAUGA	751	AUUUGAUUGU GGGAAGCCU	1151
LPA - 548 6	GUGGGAAGCCUCAAGUGGA ACCGAA	352	UUCGGUCCACUUG AGGCUUCCACAA	752	GUGGGAAGCC UCAAGUGGA	1152

LPA - 550 9	AAGAAAUGUCCUGGAAGCA AUGUAG	353	CUACAUUGCUUCCA GGACAUUUCUUCG	753	AAGAAAUGUC CUGGAAGCA	1153
LPA - 551 0	AGAAAUGUCCUGGAAGCAU AGUAGG	354	CCUACUAUGCUUCC AGGACAUUUCUUC	754	AGAAAUGUCC UGGAAGCAU	1154
LPA - 551 1	GAAAUGUCCUGGAAGCAUU AUAGGG	355	CCCUAUAUAGCUUC CAGGACAUUUCUU	755	GAAAUGUCCU GGAAGCAUU	1155
LPA - 551 3	AAUGUCCUGGAAGCAUUGU AGGGGG	356	CCCCUACAAUGCU UCCAGGACAUUUC	756	AAUGUCCUGG AAGCAUUGU	1156
LPA - 551 4	AUGUCCUGGAAGCAUUGUA AGGGGG	357	CCCCUUACAAUGC UCCAGGACAUUU	757	AUGUCCUGGA AGCAUUGUA	1157
LPA - 558 1	AGAACAAGGUUUGGAAAGC ACUUCT	358	AGAAGUGCUUCCA AACCUUGUUCUGA	758	AGAACAAGGU UUGGAAAGC	1158
LPA - 558 2	GAACAAGGUUUGGAAAGCA AUUCTG	359	CAGAAUUGCUUCC AAACCUUGUUCUG	759	GAACAAGGUU UGGAAAGCA	1159
LPA - 558 3	AACAAGGUUUGGAAAGCAC AUCUGT	360	ACAGAUGUGCUUUC CAAACCUUGUUCU	760	AACAAGGUUU GGAAAGCAC	1160
LPA - 558 4	ACAAGGUUUGGAAAGCACU ACUGTG	361	CACAGUAGUGCUUU CCAAACCUUGUUC	761	ACAAGGUUUG GAAAGCACU	1161
LPA - 558 5	CAAGGUUUGGAAAGCACUU AUGUGG	362	CCACAUAAGUGCUU UCCAAACCUUGUU	762	CAAGGUUUGG AAAGCACUU	1162
LPA - 558 6	AAGGUUUGGAAAGCACUUC AGUGGA	363	UCCACUGAAGUGCU UCCAAACCUUGU	763	AAGGUUUGGA AAGCACUUC	1163
LPA - 558 7	AGGUUUGGAAAGCACUUCU AUGGAG	364	CUCCAUAAGAAGUGC UUUCCAAACCUUG	764	AGGUUUGGAA AGCACUUCU	1164
LPA - 559 2	UGGAAAGCACUUCUGUGGA AGCACC	365	GGUGCUUCCACAGA AGUGCUUUCCAA	765	UGGAAAGCAC UUCUGUGGA	1165
LPA - 560 6	GUGGAGGCACCUUAAUAUC ACCAGA	366	UCUGGUGAUUAUA GGUGCCUCCACAG	766	GUGGAGGCAC CUUAAUAUC	1166
LPA - 561 6	CUUAAUAUCCCCAGAGUGG AUGCTG	367	CAGCAUCCACUCUG GGGAUAUUAAGGU	767	CUUAAUAUCC CCAGAGUGG	1167

LPA - 561 8	UAAUAUCCCCAGAGUGGGU ACUGAC	368	GUCAGUACCCACUC UGGGGAUAUUAAG	768	UAAUAUCCCC AGAGUGGGU	1168
LPA - 562 8	AGAGUGGGUGCUGACUGCU ACUCAC	369	GUGAGUAGCAGUCA GCACCCACUCUGG	769	AGAGUGGGUG CUGACUGCU	1169
LPA - 568 5	CAAGGUCAUCCUGGGUGCA AACCAA	370	UUGGUUUGCACCCA GGAUGACCUUGUA	770	CAAGGUCAUC CUGGGUGCA	1170
LPA - 569 4	CCUGGGUGCACACCAAGAA AUGAAC	371	GUUCAUUUCUUGGU GUGCACCCAGGAU	771	CCUGGGUGCA CACCAAGAA	1171
LPA - 569 9	GUGCACACCAAGAAGUGAA ACUCGA	372	UCGAGUUUCACUUC UUGGUGUGCACCC	772	GUGCACACCA AGAAGUGAA	1172
LPA - 577 5	AGCAGAUUUGCCUUGCUA AAGCTA	373	UAGCUUUAGCAAGG CAAUAUCUGCUUG	773	AGCAGAUUU GCCUUGCUA	1173
LPA - 577 6	GCAGAUUUGCCUUGCUAA AGCUAA	374	UUAGCUUUAGCAAG GCAAUAUCUGCUU	774	GCAGAUUUG CCUUGCUAA	1174
LPA - 577 7	CAGAUUUGCCUUGCUAAA ACUAAG	375	CUUAGUUUUAGCAA GGCAAUAUCUGCU	775	CAGAUUUGC CUUGCUAAA	1175
LPA - 577 8	AGAUAUUGCCUUGCUAAAG AUAAGC	376	GCUUAUCUUUAGCA AGGCAAUAUCUGC	776	AGAUAUUGCC UUGCUAAAG	1176
LPA - 577 9	GAUAUUGCCUUGCUAAAGC AAAGCA	377	UGC UUUGCUUUAGC AAGGCAAUAUCUG	777	GAUAUUGCCU UGC UAAAGC	1177
LPA - 578 0	AUAUUGCCUUGCUAAAGCU AAGCAG	378	CUGCUUAGCUUUAG CAAGGCAAUAUCU	778	AUAUUGCCUU GCUAAAGCU	1178
LPA - 578 1	UAUUGCCUUGCUAAAGCUA AGCAGG	379	CCUGCUUAGCUUUA GCAAGGCAAUAUC	779	UAUUGCCUUG CUAAAGCUA	1179
LPA - 581 3	UCAUCACUGACAAAGUAAU ACCAGC	380	GCUGGUUUACUUU GUCAGUGAUGACG	780	UCAUCACUGA CAAAGUAAU	1180
LPA - 587 3	GGACUGAAUGUUACAUCAC AGGCTG	381	CAGCCUGUGAUGUA ACAUUCAGUCCUG	781	GGACUGAAUG UUACAUCAC	1181
LPA - 587 4	GACUGAAUGUUACAUCACU AGCUGG	382	CCAGCUAGUGAUGU AACAUUCAGUCCU	782	GACUGAAUGU UACAUCACU	1182

LPA - 587 5	ACUGAAUGUUACAUCACUG ACUGGG	383	CCCAGUCAGUGAUG UAACAUUCAGUCC	783	ACUGAAUGUU ACAUCACUG	1183
LPA - 587 6	CUGAAUGUUACAUCACUGG AUGGGG	384	CCCCAUCCAGUGAU GUAACAUUCAGUC	784	CUGAAUGUUA CAUCACUGG	1184
LPA - 587 7	UGAAUGUUACAUCACUGGC AGGGGA	385	UCCCCUGCCAGUGA UGUAACAUUCAGU	785	UGAAUGUUAC AUCACUGGC	1185
LPA - 587 9	AAUGUUACAUCACUGGCUG AGGAGA	386	UCUCCUCAGCCAGU GAUGUAACAUUCA	786	AAUGUUAUUA CACUGGCUG	1186
LPA - 590 2	GAAACCCAAGGUACCUUG AGACTG	387	CAGUCUCAAAGGUA CCUUGGGUUUCUC	787	GAAACCCAAG GUACCUUG	1187
Con trol	Passenger (Sense)	SEQ ID NO:	Guide (Antisense)	SEQ ID NO:	Target Sequence	SEQ ID NO:
Gal XC- LPA - 367 5	GACAACAGAAUUAUCCA AGCAGCCGAAAGGCUGC	1188	UUGGAUAAUUAUCU GUUGUCGG	1189	GACAACAGAA UAUUAUCCA	1190
NC1	CGUUAUUCGCGUAUAAUAC GCGUAT	1191	AUACGCGUAUUAUA CGCGAUUAACGAC	1192	N/A	
NC5	CAUAUUGCGCGUAUAGUCG CGUUAG	1193	CUAACGCGACUAUA CGCGCAUAUUGGU	1194	N/A	
NC7	GGCGCGUAUAGUCGCGCGU AUAGTC	1195	GACUAUACGCGCGA CUAUACGCGCCUC	1196	N/A	

[0198] *In Vitro Cell-Based Assays*

[0199] The ability of each of the DsiRNAs listed in **Table 2** to inhibit *LPA* expression was determined using *in vitro* cell-based assays. Briefly, human embryonic kidney 293 (HEK293) or HepG2 cells stably expressing a human *LPA* gene were transfected with each of the DsiRNAs listed in Table 2 at 0.5 nM in separate wells of a multi-well cell-culture plate. Cells were maintained for 24 hours following transfection, and then the amount of remaining *LPA* mRNA from the transfected cells was determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3' assay and a 5' assay, were used to determine *LPA* mRNA levels as measured using PCR probes conjugated to 6-carboxyfluorescein (6-FAM).

[0200] The results of the HEK293 and HepG2 cell-based assays to evaluate the ability of the DsiRNAs listed in **Table 2** to inhibit *LPA* expression are shown in **FIGs. 1-4** and **FIG 5**, respectively. Cells transfected with a GalNAc-conjugated LPA oligonucleotide (GalXC-LPA-3675 SEQ ID NO: 1188 and 1189) were used as a positive control. DsiRNAs that resulted in

less than or equal to about 15%-20% *LPA* mRNA remaining in DsiRNA-transfected cells when compared to mock-transfected cells were generally considered to comprise sequences that provide a suitable amount of knockdown or reduction of target mRNA expression for further evaluation. In **FIGs. 1-5**, the percent of *LPA* mRNA remaining in cells transfected with DsiRNAs, as indicated, relative to time-matched control cells is shown (3' assay = circle shapes; 5' assay = triangle shapes).

[0201] To further evaluate the DsiRNA hits, a subset of the DsiRNAs listed in **Table 2** were tested to determine their ability to inhibit *LPA* expression using *in vitro* cell-based assays at two different DsiRNA concentrations (**FIG. 6** and **FIG. 7**). Briefly, HEK293 cells stably expressing a human *LPA* gene were transfected with DsiRNAs at 0.1 nM and 0.5 nM in separate wells of a multi-well cell-culture plate. Cells were maintained for 24 hr. following transfection, and then the amount of remaining *LPA* mRNA from the transfected cells was determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3' assay and a 5' assay, were used to determine *LPA* mRNA levels as measured using PCR probes conjugated to hexachloro-fluorescein (HEX). Untransfected cells (UT), mock-transfected cells (Mock), and cells transfected with control oligonucleotides (NC1, SEQ ID NOs: 1191 and 1192; NC5, SEQ ID NO: 1193 and 1194; and NC7, SEQ ID NO: 1195 and 1196) were used as negative controls. As shown in **FIGs. 6** and **7**, the percent of *LPA* mRNA remaining in HEK293 cells transfected with the indicated DsiRNAs is an average of the *LPA* mRNA levels from the 3' assay and 5' assay and is normalized to time-matched, mock-transfected control HEK293 cells.

[0202] Taken together, these results show that DsiRNAs designed to target human *LPA* mRNA inhibit *LPA* expression in cells, as determined by a reduced amount of *LPA* mRNA in DsiRNA-transfected cells relative to control cells. These results demonstrate that the nucleotide sequences comprising the DsiRNA are useful for generating RNAi oligonucleotides to inhibit *LPA* expression. Further, these results demonstrate that multiple *LPA* mRNA target sequences are suitable for the RNAi-mediated inhibition of *LPA* expression.

Example 3: RNAi Oligonucleotide Inhibition of *LPA* Expression *In Vivo*

[0203] Of the DsiRNAs screened in the cell-based assays described in **Example 2**, the nucleotide sequences of 14 DsiRNAs were selected for further evaluation *in vivo*. Briefly, the nucleotide sequences of the 14 selected DsiRNAs were used to generate 14 corresponding double-stranded RNAi oligonucleotides comprising a nicked tetraloop GalNAc-conjugated structure (referred to herein as “GalNAc-conjugated *LPA* oligonucleotides”) having a 36-mer passenger strand and a 22-mer guide strand (**Table 3**). Further, the nucleotide sequences

comprising the passenger strand and guide strand of the GalNAc-conjugated *LPA* oligonucleotides have a distinct pattern of modified nucleotides and phosphorothioate linkages (*e.g.*, see **FIG. 10** for a schematic of the generic structure and chemical modification patterns (M1, M2, and M3) of the GalNAc-conjugated *LPA* oligonucleotides). The three adenosine nucleotides comprising the tetraloop are each conjugated to a GalNAc moiety (CAS#: 14131-60-3).

[0204] Table 3: GalNAc-Conjugated *LPA* Oligonucleotides Evaluated in Mice

Oligonucleotide	DP#	SEQ ID NO (Sense)	SEQ ID NO (Antisense)
LPA-0190-M1	DP15791P:DP15790G	388	788
LPA-0501-M1	DP15634P:DP15633G	389	789
LPA-3100-M1	DP15639P:DP15638G	390	790
LPA-3286-M1	DP15643P:DP15642G	391	791
LPA-3288-M1	DP15645P:DP15644G	392	792
LPA-3291-M1	DP15647P:DP15646G	393	793
LPA-3584-M1	DP15651P:DP15650G	394	794
LPA-3585-M1	DP15653P:DP15652G	395	795
LPA-4645-M1	DP15657P:DP15656G	396	796
LPA-4717-M1	DP15801P:DP15800G	397	797
LPA-5510-M1	DP15815P:DP15814G	398	798
LPA-3750-M1	DP13346P:DP13385G	399	799
LPA-2900-M2	DP13351P:DP14623G	400	800
LPA-3675-M2	DP13346P:DP14624G	401	801
LPA-2900-M3	DP13351P:DP13387G	402	802
LPA-3675-M3	DP13346P:DP13385G	403	803

[0205] Mouse Studies

[0206] The GalNAc-conjugated *LPA* oligonucleotides listed in **Table 3** were evaluated in an HDI mouse model, wherein HDI mice were engineered to transiently express human *LPA* mRNA in hepatocytes. The GalNAc-conjugated *LPA* oligonucleotide LPA-3675-M2 was used as a benchmark control. Briefly, 6-8-week-old female CD-1 mice ($n = 5$) were treated subcutaneously with the indicated GalNAc-conjugated *LPA* oligonucleotides at a dose level of 0.5 mg/kg (**FIG. 8**) or at a dose level of 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg (**FIG. 9**). Three days later (72 h), the mice were hydrodynamically injected (HDI) with a DNA plasmid encoding the full human *LPA* gene under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after introduction of the DNA plasmid, liver samples from mice

were collected. Total RNA derived from these mice were subjected to qRT-PCR analysis for *LPA* mRNA, relative to mice treated only with an identical volume of PBS. The values were normalized for transfection efficiency using the NeoR gene included on the plasmid.

[0207] As shown in **FIG. 8**, the indicated GalNAc-conjugated *LPA* oligonucleotides inhibited *LPA* expression, as determined by a reduction in the amount of *LPA* mRNA in liver samples from oligonucleotide-treated HDI mice relative to mice treated with PBS. To further evaluate the ability of GalNAc-conjugated *LPA* oligonucleotides to inhibit *LPA* expression, two of the GalNAc-conjugated *LPA* oligonucleotide sequences (LPA-2900 and LPA-3675) each having a different chemical modification pattern (M2 and M3) were tested for their ability to inhibit *LPA* expression in the HDI mice described above at three different concentrations (0.25 mg/kg, 0.5 mg/kg, and 1.0 mg/kg). As shown in **FIG. 9**, the indicated GalNAc-conjugated *LPA* oligonucleotides inhibited *LPA* expression in HDI mice in a dose-dependent manner.

[0208] Taken together, these results show that GalNAc-conjugated *LPA* oligonucleotides designed to target human *LPA* mRNA inhibit *LPA* expression in mice, as determined by a reduction in the amount of *LPA* mRNA in HDI mouse livers relative to control mice treated with PBS. Based on these results, 10 of the 14 GalNAc-conjugated *LPA* oligonucleotides evaluated in HDI mice were selected for evaluation of their ability to inhibit *LPA* expression in non-human primates (NHPs). The 10 GalNAc-conjugated *LPA* oligonucleotides listed in **Table 4** comprise chemically modified nucleotides having pattern M1, M2, or M3 as described in **FIG. 10**.

[0209] **Table 4:** GalNAc-Conjugated *LPA* Oligonucleotides Evaluated in NHPs

Oligonucleotide	DP#	SEQ ID NO (Sense)	SEQ ID NO (Antisense)
LPA-0190-M1	DP15791P:DP15790G	388	788
LPA-3100-M1	DP15639P:DP15638G	390	790
LPA-3288-M1	DP15645P:DP15644G	392	792
LPA-3291-M1	DP15647P:DP15646G	393	793
LPA-3585-M1	DP15653P:DP15652G	395	795
LPA-4645-M1	DP15657P:DP15656G	396	796
LPA-4717-M1	DP15801P:DP15800G	397	797
LPA-5510-M1	DP15815P:DP15814G	398	798
LPA-2900-M2	DP13351P:DP14623G	400	800
LPA-3675-M3	DP13346P:DP13385G	403	803

[0210] *Non-Human Primate (NHP) Studies*

[0211] The GalNAc-conjugated *LPA* oligonucleotides listed in **Table 4** were evaluated in cynomolgus monkeys (*Macaca fascicularis*). In this study, the monkeys are grouped so that their mean body weights (about 5.4 kg) are comparable between the control and experimental groups. Each cohort contains two male and three female subjects. The GalNAc-conjugated *LPA* oligonucleotides were administered subcutaneously on Study Day 0. Blood samples were collected on Study Days -8, -5 and 0, and weekly after dosing. Ultrasound-guided core needle liver biopsies were collected on Study Days 28, 56 and 84. At each time point, total RNA derived from the liver biopsy samples was subjected to qRT-PCR analysis to measure *LPA* mRNA in oligonucleotide-treated monkeys relative to monkeys treated with a comparable volume of PBS. To normalize the data, the measurements were made relative to the geometric mean of two reference genes, PPIB and 18S rRNA. As shown in **FIG. 11A** (Day 28), **FIG. 11B** (Day 56), and **FIG. 11C** (Day 84), treatment of NHPs with the GalNAc-conjugated *LPA* oligonucleotides listed in **Table 4** inhibited *LPA* expression in the liver, as determined by a reduction in the amount of *LPA* mRNA in liver samples from oligonucleotide-treated NHPs relative to NHPs treated with PBS. The amount of plasminogen (PLG) mRNA in the liver samples of treated NHPs was also determined and is shown in **FIG. 11D**. From the same NHP study, inhibition of *LPA* expression was also determined by measuring apo(a) protein serum from treated NHPs by ELISA. As shown in **FIG. 12**, a significant reduction in serum apo(a) protein was observed in NHPs treated with GalNAc-conjugated *LPA* oligonucleotides compared to NHPs treated with PBS. Values from three pre-dose samples are averaged and set to 100%, and data are reported as relative values compared to the pre-dose average. Taken together, these results demonstrate that treatment of NHPs with GalNAc-conjugated *LPA* oligonucleotides reduced the amount of *LPA* mRNA in the liver and reduced the amount of apo(a) protein in the serum.

[0212] Taken together, these results show that GalNAc-conjugated *LPA* oligonucleotides designed to target human *LPA* mRNA inhibit *LPA* expression *in vivo* (as determined by the reduction of the amount of *LPA* mRNA and apo(a) protein in treated animals).

SEQUENCE LISTING

[0213] The following nucleic and/or amino acid sequences are referred to in the disclosure above and are provided below for reference.

[0214] **Table 5: LPA Oligonucleotide Sequences (Unmodified)**

Oligonucleotide	Sequence (Sense Strand)	SEQ ID NO:	Sequence (Antisense Strand)	SEQ ID NO:
LPA-125	CUGAGCAAAGCCAUGUGGUAC AGGA	4	UCCUGUACCACAUGGCUUUGC UCA	404
LPA-128	AGCAAAGCCAUGUGGUCCAAG AUTG	5	CAAUCUUGGACCACAUGGCUU UUG	405
LPA-132	AAGCCAUGUGGUCCAGGAUAG CUAC	6	GUAGCUAUCCUGGACCACAUG GCU	406
LPA-133	AGCCAUGUGGUCCAGGAUUAC UACC	7	GGUAGUAAUCCUGGACCACA UUG	407
LPA-134	GCCAUGUGGUCCAGGAUUGAU ACCA	8	UGGUAUCAUCCUGGACCACA UUG	408
LPA-135	CCAUGUGGUCCAGGAUUGCAA CCAT	9	AUGGUUGCAAUCCUGGACCACA UUG	409
LPA-136	CAUGUGGUCCAGGAUUGCUAC CATG	10	CAUGGUAGCAAUCCUGGACCACA UUG	410
LPA-137	AUGUGGUCCAGGAUUGCUAAC AUGG	11	CCAUGUUAGCAAUCCUGGACCACA UUG	411
LPA-138	UGUGGUCCAGGAUUGCUACAA UGGT	12	ACCAUUGUAGCAAUCCUGGACCACA UUG	412
LPA-160	GGUGAUGGACAGAGUUAUCAA GGCA	13	UGCCUUGAUAAUCCUGUCCAUCAC CAU	413
LPA-190	UCCACCACUGUCACAGGAAAG ACCT	14	AGGUCUUUCCUGUGACAGUGGUGG AGU	414
LPA-191	CCACCACUGUCACAGGAAGAA CCTG	15	CAGGUUCUCCUGUGACAGUGGUGG GAG	415
LPA-197	CUGUCACAGGAAGGACCUGAC AAGC	16	GCUUGUCAGGUCCUCCUGUGACA GUG	416
LPA-205	GGAAGGACCUGCCAAGCUUAG UCAT	17	AUGACUAAGCUUGGCAGGUCCUUC CUG	417
LPA-206	GAAGGACCUGCCAAGCUUGAU CATC	18	GAUGAUCAAGCUUGGCAGGUCCU CCU	418
LPA-208	AGGACCUGCCAAGCUUGGUAA UCTA	19	UAGAUUACCAAGCUUGGCAGGUCC UUC	419
LPA-209	GGACCUGCCAAGCUUGGUCAU CUAT	20	AUAGAUGACCAAGCUUGGCAGGUCC CUU	420
LPA-210	GACCUGCCAAGCUUGGUCAAC UATG	21	CAUAGUUGACCAAGCUUGGCAGGU CCU	421
LPA-211	ACCUGCCAAGCUUGGUCAUAA AUGA	22	UCAUAUAUGACCAAGCUUGGCAGG UCC	422
LPA-212	CCUGCCAAGCUUGGUCAUCAA UGAC	23	GUCAUUGAUGACCAAGCUUGGCAG GUC	423
LPA-219	AGCUUGGUCAUCUAUGACAAC ACAT	24	AUGUGUUGUCAUAGAUGACCAAGC UUG	424

LPA-225	GUCAUCUAUGACACCACAUA ACAT	25	AUGUUUAUGUGGUGUCAUAGA CCA	425
LPA-258	CACAGAAAACUACCCAAAUAC UGGC	26	GCCAGUAUUUGGGUAGUUUCUG GGU	426
LPA-261	AGAAAACUACCCAAAUAGCUAG CUTG	27	CAAGCUAGCAUUUGGGUAGUUUC UGU	427
LPA-263	AAAACUACCCAAAUAGCUGGAU UGAT	28	AUCAAUCCAGCAUUUGGGUAGUU UCU	428
LPA-269	ACCCAAAUAGCUGGCUUGAUAA UGAA	29	UUCAUUAUCAAGCCAGCAUUUGG UAG	429
LPA-270	CCCAAUAGCUGGCUUGAUCAU GAAC	30	GUUCAUGAUCAAGCCAGCAUUUG GUA	430
LPA-291	GAACUACUGCAGGAUCCAAA UGCT	31	AGCAUUUGGAUUCUGCAGUAGU CAU	431
LPA-295	UACUGCAGGAUCCAGAUAGAU GUGG	32	CCACAUCAUCUGGAUUCUGCAGU AGU	432
LPA-296	ACUGCAGGAUCCAGAUAGCAG UGGC	33	GCCACUGCAUCUGGAUUCUGCAG UAG	433
LPA-298	UGCAGGAUCCAGAUAGCUGAG GCAG	34	CUGCCUCAGCAUCUGGAUUCUGC AGU	434
LPA-355	AGGUGGGAGUACUGCAACCAG ACGC	35	GCGUCUGGUUGCAGUACUCCACC UGA	435
LPA-380	AAUGCUCAGACGCAGAAGGAA CUGC	36	GCAGUUCUUCUGCGUCUGAGCAU UGC	436
LPA-417	GACUGUUACCCCGGUUCCAAG CCTA	37	UAGGCUUGGAACCGGGGUAACAGU CGG	437
LPA-418	ACUGUUACCCCGGUUCCAAC CUAG	38	CUAGGUUUGGAACCGGGGUAACAG UCG	438
LPA-419	CUGUUACCCCGGUUCCAAGAC UAGA	39	UCUAGUCUUGGAACCGGGGUAACA GUC	439
LPA-420	UGUUACCCCGGUUCCAAGCAU AGAG	40	CUCUAUGCUUGGAACCGGGGUAAC AGU	440
LPA-421	GUUACCCCGGUUCCAAGCCAA GAGG	41	CCUCUUGGCUUGGAACCGGGGUA CAG	441
LPA-422	UUACCCCGGUUCCAAGCCUAG AGGC	42	GCCUCUAGGCUUGGAACCGGGGUA ACA	442
LPA-423	UACCCCGGUUCCAAGCCUAAA GGCT	43	AGCCUUUAGGCUUGGAACCGGGGU AAC	443
LPA-492	GUGCUACCAUGGUAAUGGAAA GAGT	44	ACUCUUUCCAUAUACCAUGGUAGCA CUC	444
LPA-493	UGCUACCAUGGUAAUGGACAG AGTT	45	AACUCUGUCCAUAUACCAUGGUAGC ACU	445
LPA-494	GCUACCAUGGUAAUGGACAAA GUTA	46	UAACUUUGUCCAUAUACCAUGGUAG CAC	446
LPA-495	CUACCAUGGUAAUGGACAGAG UUAT	47	AUAACUCUGUCCAUAUACCAUGGUA GCA	447
LPA-496	UACCAUGGUAAUGGACAGAAU UATC	48	GAUAAUUCUGUCCAUAUACCAUGGU AGC	448
LPA-497	ACCAUGGUAAUGGACAGAGAU AUCG	49	CGAUUAUCUCUGUCCAUAUACCAUGG UAG	449
LPA-498	CCAUGGUAAUGGACAGAGUAA UCGA	50	UCGAUUACUCUGUCCAUAUACCAUG GUA	450

LPA-499	CAUGGUAUUGGACAGAGUUU CGAG	51	CUCGAUAACUCUGUCCAUAUACCAU GGU	451
LPA-500	AUGGUAUUGGACAGAGUUUAC GAGG	52	CCUCGUUAACUCUGUCCAUAUACCA UGG	452
LPA-501	UGGUAUUGGACAGAGUUUAG AGGC	53	GCCUCUAUAACUCUGUCCAUAUACC AUG	453
LPA-502	GGUAUUGGACAGAGUUUAUCAA GGCA	54	UGCCUUGAUAAACUCUGUCCAUAUAC CAU	454
LPA-503	GUAAUGGACAGAGUUUACGAG GCAC	55	GUGCCUCGAUAACUCUGUCCAUAUA CCA	455
LPA-523	GGCACAUAUCCACCACUGAC ACAG	56	CUGUGUCAGUGGUGGAGUAUGUGC CUC	456
LPA-563	CUUGGUCAUCUAUGACACCAC ACTC	57	GAGUGUGGUGUCAUAGAUGACCAA GCU	457
LPA-567	GUCAUCUAUGACACCACACAC GCAT	58	AUGCGUGUGUGGUGUCAUAGAUGA CCA	458
LPA-568	UCAUCUAUGACACCACACUAG CATA	59	UAUGCUAGUGUGGUGUCAUAGAUG ACC	459
LPA-569	CAUCUAUGACACCACACUCAC AUAG	60	CUAUGUGAGUGUGGUGUCAUAGAU GAC	460
LPA-1208	GCACAUAUCCACCACUGUAA CUGG	61	CCAGUUAACAGUGGUGGAGUAUGUG CCU	461
LPA-2715	AGCCCCUUAUUGUUUAUACGAG GGAT	62	AUCCCUUGUAUAACAAUAAGGGGC UGC	462
LPA-2716	GCCCCUUAUUGUUUAUACGAAG GATC	63	GAUCCUUCGUUAACAAUAAGGGG CUG	463
LPA-2827	CCAAGCCUAGAGGCUCUUUAU GAAC	64	GUUCAUAAGGAGCCUCUAGGCUUG GAA	464
LPA-2837	AGGCUCUUCUGAACAAGCAC CAAC	65	GUUGGUGCUUGUUCAGAAGGAGCC UCU	465
LPA-2900	AUGGACAGAGUUUAUCAAGGAA CATA	66	UAUGUCCUUGAUAAACUCUGUCCA UUU	466
LPA-2901	UGGACAGAGUUUAUCAAGGCAC AUAC	67	GUAUGUGCCUUGAUAAACUCUGUCC AUU	467
LPA-2902	GGACAGAGUUUAUCAAGGCAAA UACT	68	AGUAUUUGCCUUGAUAAACUCUGUC CAU	468
LPA-2903	GACAGAGUUUAUCAAGGCACAU ACTT	69	AAGUAUGUGCCUUGAUAAACUCUGU CCA	469
LPA-2904	ACAGAGUUUAUCAAGGCACAAA CUTC	70	GAAGUUUGGCCUUGAUAAACUCUG UCC	470
LPA-2905	CAGAGUUUAUCAAGGCACAUAC UUCA	71	UGAAGUAUGUGCCUUGAUAAACUCU GUC	471
LPA-3004	UACCCAAAUGCUGGCUUGAAC AAGA	72	UCUUGUUAAGCCAGCAUUUGGGU AGU	472
LPA-3007	CCAAAUGCUGGCUUGAUCAAG AACT	73	AGUUCUUGAUCAAGCCAGCAUUUG GGU	473
LPA-3023	UCAAGAACUACUGCCGAAAAC CAGA	74	UCUGGUUUUCGGCAGUAGUUCUUG AUC	474
LPA-3024	CAAGAACUACUGCCGAAAUAUAC AGAT	75	AUCUGUAUUUCGGCAGUAGUUCUU GAU	475
LPA-3025	AAGAACUACUGCCGAAAUCAA GATC	76	GAUCUUGAUUUUCGGCAGUAGUUCU UGA	476

LPA-3027	GAACUACUGCCGAAAUCCAAA UCCT	77	AGGAUUUGGAUUUCGGCAGUAGUU CUU	477
LPA-3030	CUACUGCCGAAAUCCAGAUAC UGTG	78	CACAGUAUCUGGAUUUCGGCAGUA GUU	478
LPA-3051	UGUGGCAGCCCCUUGGUGUAA UACA	79	UGUAUUACACCAAGGGGCUGCCAC AGG	479
LPA-3052	GUGGCAGCCCCUUGGUGUUAU ACAA	80	UUGUAUAACACCAAGGGGCUGCCA CAG	480
LPA-3053	UGGCAGCCCCUUGGUGUUAAA CAAC	81	GUUGUUUAACACCAAGGGGCUGCC ACA	481
LPA-3054	GGCAGCCCCUUGGUGUUAUAC AACA	82	UGUUGUAUAACACCAAGGGGCUGC CAC	482
LPA-3055	GCAGCCCCUUGGUGUUUAAAA ACAG	83	CUGUUUUUAACACCAAGGGGCUG CCA	483
LPA-3056	CAGCCCCUUGGUGUUUAUACAA CAGA	84	UCUGUUGUAUAACACCAAGGGGCU GCC	484
LPA-3057	AGCCCCUUGGUGUUUAUACAAC AGAT	85	AUCUGUUGUAUAACACCAAGGGGC UGC	485
LPA-3058	GCCCCUUGGUGUUUAUACAAAA GATC	86	GAUCUUUUGUAUAACACCAAGGGG CUG	486
LPA-3059	CCCCUUGGUGUUUAUACAACAG AUCC	87	GGAUCUGUUGUAUAACACCAAGGG GCU	487
LPA-3092	GGUGGGAGUACUGCAACCUAA CACG	88	CGUGUUAGGUUGCAGUACUCCAC CUG	488
LPA-3093	GUGGGAGUACUGCAACCUGAC ACGA	89	UCGUGUCAGGUUGCAGUACUCCCA CCU	489
LPA-3096	GGAGUACUGCAACCUGACAAG AUGC	90	GCAUCUUGUCAGGUUGCAGUACUC CCA	490
LPA-3097	GAGUACUGCAACCUGACACAA UGCT	91	AGCAUUGUGUCAGGUUGCAGUACU CCC	491
LPA-3099	GUACUGCAACCUGACACGAAG CUCA	92	UGAGCUUCGUGUCAGGUUGCAGUA CUC	492
LPA-3100	UACUGCAACCUGACACGAUAC UCAG	93	CUGAGUAUCGUGUCAGGUUGCAGU ACU	493
LPA-3101	ACUGCAACCUGACACGAUGAU CAGA	94	UCUGAUCAUCGUGUCAGGUUGCAG UAC	494
LPA-3102	CUGCAACCUGACACGAUGCAC AGAT	95	AUCUGUGCAUCGUGUCAGGUUGCA GUA	495
LPA-3103	UGCAACCUGACACGAUGCUGAA GATG	96	CAUCUUAGCAUCGUGUCAGGUUGC AGU	496
LPA-3105	CAACCUGACACGAUGCUGAAA UGCA	97	UGCAUUUGAGCAUCGUGUCAGGUU GCA	497
LPA-3107	ACCUGACACGAUGCUCAGAAG CAGA	98	UCUGCUUCGAGCAUCGUGUCAGG UUG	498
LPA-3108	CCUGACACGAUGCUCAGAUAC AGAA	99	UUCUGUAUCGAGCAUCGUGUCAG GUU	499
LPA-3109	CUGACACGAUGCUCAGAUAA GAAT	100	AUUCUUCAUCGAGCAUCGUGUCA GGU	500
LPA-3110	UGACACGAUGCUCAGAUACAG AATG	101	CAUUCUGCAUCGAGCAUCGUGUC AGG	501
LPA-3111	GACACGAUGCUCAGAUCAAAA AUGG	102	CCAUUUUGCAUCGAGCAUCGUGU CAG	502

LPA-3112	ACACGAUGCUCAGAU GCAGAA UGGA	103	UCCAUUCUGCAUCUGAGCAUCGUG UCA	503
LPA-3113	CACGAUGCUCAGAU GCAGAAU GGAC	104	GUCCAUUCUGCAUCUGAGCAUCGU GUC	504
LPA-3229	UGCUCUACCAUUAUGGACAG AGTT	105	AACUCUGUCCAUA AUGGUAGUAGC AGU	505
LPA-3230	GCUACUACCAUUAUGGACAAA GUTA	106	UAACUUUGUCCAUA AUGGUAGUAG CAG	506
LPA-3231	CUACUACCAUUAUGGACAGAG UUAC	107	GUAACUCUGUCCAUA AUGGUAGUA GCA	507
LPA-3232	UACUACCAUUAUGGACAGAAU UACC	108	GGUAAUUCUGUCCAUA AUGGUAGU AGC	508
LPA-3233	ACUACCAUUAUGGACAGAGAU ACCG	109	CGGUAUUCUGUCCAUA AUGGUAG UAG	509
LPA-3234	CUACCAUUAUGGACAGAGUAA CCGA	110	UCGGUUAUCUGUCCAUA AUGGU GUA	510
LPA-3235	UACCAUUAUGGACAGAGUUAC CGAG	111	CUCGGUAACUCUGUCCAUA AUGGU AGU	511
LPA-3236	ACCAUUAUGGACAGAGUUAAC GAGG	112	CCUCGUUAACUCUGUCCAUA AUGG UAG	512
LPA-3257	GAGGCACAUACUCCACCACAG UCAC	113	GUGACUGUGGUGGAGUAUGUGCCU CGG	513
LPA-3267	CUCCACCACUGUCACAGGAAG AACT	114	AGUUCUCCUGUGACAGUGGUGGA GUA	514
LPA-3280	ACAGGAAGAACUUGCCAAGAU UGGT	115	ACCAAUCUUGGCAAGUUCUCCUG UGA	515
LPA-3281	CAGGAAGAACUUGCCAAGCAU GGTC	116	GACCAUGCUUGGCAAGUUCUCCU GUG	516
LPA-3282	AGGAAGAACUUGCCAAGCUAG GUCA	117	UGACCUAGCUUGGCAAGUUCUCC UGU	517
LPA-3283	GGAAGAACUUGCCAAGCUUAG UCAT	118	AUGACUAAGCUUGGCAAGUUCUUC CUG	518
LPA-3284	GAAGAACUUGCCAAGCUUGAU CATC	119	GAUGAUCAAGCUUGGCAAGUUCU CCU	519
LPA-3285	AAGAACUUGCCAAGCUUGGAC AUCT	120	AGAUGUCCAAGCUUGGCAAGUUCU UCC	520
LPA-3286	AGAACUUGCCAAGCUUGGUAA UCTA	121	UAGAUUACCAAGCUUGGCAAGUUC UUC	521
LPA-3287	GAACUUGCCAAGCUUGGUCAU CUAT	122	AUAGAUGACCAAGCUUGGCAAGUU CUU	522
LPA-3288	AACUUGCCAAGCUUGGUCAAC UATG	123	CAUAGUUGACCAAGCUUGGCAAGU UCU	523
LPA-3289	ACUUGCCAAGCUUGGUCAUAU AUGA	124	UCAUAUAUGACCAAGCUUGGCAAG UUC	524
LPA-3290	CUUGCCAAGCUUGGUCAUCAA UGAC	125	GUCAUUGAUGACCAAGCUUGGCAA GUU	525
LPA-3291	UUGCCAAGCUUGGUCAUCUAU GACA	126	UGUCAUAGAUGACCAAGCUUGGCA AGU	526
LPA-3292	UGCCAAGCUUGGUCAUCUAAG ACAC	127	GUGUCUUAGAUGACCAAGCUUGGC AAG	527
LPA-3298	GCUUGGUCAUCUAUGACACAA CACC	128	GGUGUUGUGUCAUAGAUGACCAAG CUU	528

LPA-3300	UUGGUCAUCUAUGACACCAAA CCAG	129	CUGGUUUGGUGUCAUAGAUGACCA AGC	529
LPA-3301	UGGUCAUCUAUGACACCACAC CAGC	130	GCUGGUGUGGUGUCAUAGAUGACC AAG	530
LPA-3303	GUCAUCUAUGACACCACACAA GCAT	131	AUGCUUGUGUGGUGUCAUAGAUGA CCA	531
LPA-3305	CAUCUAUGACACCACACCAAC AUAG	132	CUAUGUUGGUGUGGUGUCAUAGAU GAC	532
LPA-3306	AUCUAUGACACCACACCAGAA UAGT	133	ACUAUUCUGGUGUGGUGUCAUAGA UGA	533
LPA-3308	CUAUGACACCACACCAGCAAA GUCG	134	CGACUUUGCUGGUGUGGUGUCAUA GAU	534
LPA-3329	GUCGGACCCCAGAAAACUAAC CAAA	135	UUUGGUUAGUUUUCUGGGGUCCGA CUA	535
LPA-3330	UCGGACCCCAGAAAACUACAC AAAT	136	AUUUGUGUAGUUUUCUGGGGUCCG ACU	536
LPA-3340	GAAAACUACCCAAUUGCUGAC CUGA	137	UCAGGUCAGCAUUUGGGUAGUUUU CUG	537
LPA-3391	GCUGAGAUUCGCCCUUGGUU UACA	138	UGUAAUACCAAGGGCGAAUCUCAG CAU	538
LPA-3392	CUGAGAUUCGCCCUUGGUGAU ACAC	139	GUGUAUCACCAAGGGCGAAUCUCA GCA	539
LPA-3394	GAGAUUCGCCCUUGGUGUUAC ACCA	140	UGGUGUAACACCAAGGGCGAAUCU CAG	540
LPA-3395	AGAUUCGCCCUUGGUGUUA CCAT	141	AUGGUUUAACACCAAGGGCGAAUC UCA	541
LPA-3398	UUCGCCCUUGGUGUACACAA UGGA	142	UCCAUGUGUAACACCAAGGGCGA AUC	542
LPA-3404	CUUGGUGUACACCAUGGAAC CCAG	143	CUGGGUCCAUGGUGUAACACCAA GGG	543
LPA-3405	UUGGUGUACACCAUGGAUAC CAGT	144	ACUGGUAUCCAUGGUGUAACACCA AGG	544
LPA-3406	UGGUGUACACCAUGGAUCAC AGTG	145	CACUGUGAUCCAUGGUGUAACACC AAG	545
LPA-3407	GGUGUACACCAUGGAUCCAA GUGT	146	ACACUUGGAUCCAUGGUGUAACAC CAA	546
LPA-3409	UGUACACCAUGGAUCCAAU GUCA	147	UGACAUUGGGAUCCAUGGUGUAAC ACC	547
LPA-3472	GAAUCAAGUGUCCUUGCAAAU CUCA	148	UGAGAUUUGCAAGGACACUUGAU CUG	548
LPA-3473	AAUCAAGUGUCCUUGCAACAC UCAC	149	GUGAGUGUUGCAAGGACACUUGAU UCU	549
LPA-3474	AUCAAGUGUCCUUGCAACU CACG	150	CGUGAUAGUUGCAAGGACACUUGA UUC	550
LPA-3584	AUGGACAGAGUUAUCGAGGAU CATT	151	AAUGAUCCUCGAUAACUCUGUCCA UCA	551
LPA-3585	UGGACAGAGUUAUCGAGGCAC AUTC	152	GAAUGUGCCUCGAUAACUCUGUCC AUC	552
LPA-3655	ACACCACACUGGCAUCAGAAG ACAA	153	UUGUCUUCUGAUGCCAGUGUGGUG UCA	553
LPA-3747	UUGGUGUUAUACCAUGGAUAC CAAT	154	AUUGGUAUCCAUGGUAUAACACCA AGG	554

LPA-3748	UGGUGUUAUACCAUGGAUCAC AATG	155	CAUUGUGAUCCAUGGUUAUACACC AAG	555
LPA-3749	GGUGUUAUACCAUGGAUCCAA AUGT	156	ACAUUUGGAUCCAUGGUUAUACAC CAA	556
LPA-3750	GUGUUAUACCAUGGAUCCCAA UGTC	157	GACAUUGGGAUCCAUGGUUAUACA CCA	557
LPA-3773	UCAGAUGGGAGUACUGCAAAC UGAC	158	GUCAGUUUGCAGUACUCCCAUCUG ACA	558
LPA-3776	GAUGGGAGUACUGCAACCUGAA CACA	159	UGUGUUAGGUUGCAGUACUCCCAU CUG	559
LPA-3777	AUGGGAGUACUGCAACCUGAC ACAA	160	UUGUGUCAGGUUGCAGUACUCCCA UCU	560
LPA-3778	UGGGAGUACUGCAACCUGAAA CAAT	161	AUUGUUUCAGGUUGCAGUACUCCC AUC	561
LPA-3779	GGGAGUACUGCAACCUGACAC AATG	162	CAUUGUGUCAGGUUGCAGUACUCC CAU	562
LPA-3840	GGCUGUUUCUGAACAAGCAAC AACG	163	CGUUGUUGCUUGUUCAGAAACAGC CGU	563
LPA-3844	GUUUCUGAACAAGCACCAAAG GAGC	164	GCUCCUUUGGUGCUUGUUCAGAAA CAG	564
LPA-3927	CUCCACCACUGUUACAGGAAG GACA	165	UGUCCUCCUGUAACAGUGGUGGA GAA	565
LPA-3928	UCCACCACUGUUACAGGAAG ACAT	166	AUGUCUUCCUGUAACAGUGGUGG AGA	566
LPA-3929	CCACCACUGUUACAGGAAGAA CATG	167	CAUGUUCUCCUGUAACAGUGGUG GAG	567
LPA-3972	GACACCACACUGGCAUCAGAG AACC	168	GGUUCUCUGAUGCCAGUGUGGUGU CAU	568
LPA-3973	ACACCACACUGGCAUCAGAAA ACCA	169	UGGUUUUCUGAUGCCAGUGUGGUG UCA	569
LPA-3999	AGAAUACUACCCAAAUGGUAG CCTG	170	CAGGCUACCAUUUGGGUAGUAUUC UGU	570
LPA-4000	GAAUACUACCCAAAUGGUGAC CUGA	171	UCAGGUCACCAUUUGGGUAGUAU CUG	571
LPA-4001	AAUACUACCCAAAUGGUGGAC UGAC	172	GUCAGUCCACCAUUUGGGUAGUAU UCU	572
LPA-4185	UCCUUCUGAAGAAGCACCAAC UGAA	173	UUCAGUUGGUGCUUCUUCAGAAG AAG	573
LPA-4186	CCUUCUGAAGAAGCACCAAAU GAAA	174	UUUCAUUUGGUGCUUCUUCAGAAG GAA	574
LPA-4187	CUUCUGAAGAAGCACCAACAG AAAA	175	UUUUCUGUUGGUGCUUCUUCAGAA GGA	575
LPA-4188	UUCUGAAGAAGCACCAACUAA AAAC	176	GUUUUUAGUUGGUGCUUCUUCAGA AGG	576
LPA-4189	UCUGAAGAAGCACCAACUGAA AACA	177	UGUUUUCAGUUGGUGCUUCUUCAG AAG	577
LPA-4190	CUGAAGAAGCACCAACUGAAA ACAG	178	CUGUUUUCAGUUGGUGCUUCUUCA GAA	578
LPA-4191	UGAAGAAGCACCAACUGAAAA CAGC	179	GCUGUUUUCAGUUGGUGCUUCUUC AGA	579
LPA-4192	GAAGAAGCACCAACUGAAAAAC AGCA	180	UGCUGUUUUCAGUUGGUGCUUCU CAG	580

LPA-4193	AAGAAGCACCAACUGAAAAA GCAC	181	GUGCUUUUUUCAGUUGGUGCUUC UCA	581
LPA-4194	AGAAGCACCAACUGAAAAACAG CACT	182	AGUGCUGUUUUUCAGUUGGUGCUUC UUC	582
LPA-4195	GAAGCACCAACUGAAAAACAAC ACTG	183	CAGUGUUGUUUUUCAGUUGGUGCUU CUU	583
LPA-4196	AAGCACCAACUGAAAAACAGAA CUGG	184	CCAGUUCUGUUUUUCAGUUGGUGCU UCU	584
LPA-4239	AGGUGAUGGACAGAGUUUAUAG AGGC	185	GCCUCUAUAACUCUGUCCAUCACC UCG	585
LPA-4269	CUCCACCACUAUCACAGGAAG AACA	186	UGUUCUCCUGUGAUAGUGGUGGA GAG	586
LPA-4270	UCCACCACUAUCACAGGAAAA ACAT	187	AUGUUUUUCCUGUGAUAGUGGUGG AGA	587
LPA-4271	CCACCACUAUCACAGGAAGAA CATG	188	CAUGUUCUCCUGUGAUAGUGGUG GAG	588
LPA-4272	CACCACUAUCACAGGAAGAAC AUGT	189	ACAUGUUCUCCUGUGAUAGUGGU GGA	589
LPA-4273	ACCACUAUCACAGGAAGAAAA UGTC	190	GACAUUUUCUCCUGUGAUAGUGG UGG	590
LPA-4274	CCACUAUCACAGGAAGAACA GUCA	191	UGACAUGUUCUCCUGUGAUAGUG GUG	591
LPA-4275	CACUAUCACAGGAAGAACAAG UCAG	192	CUGACUUGUUCUCCUGUGAUAGU GGU	592
LPA-4276	ACUAUCACAGGAAGAACAUAU CAGT	193	ACUGAUUGUUCUCCUGUGAUAG UGG	593
LPA-4277	CUAUCACAGGAAGAACAUGAC AGTC	194	GACUGUCAUGUUCUCCUGUGAUA GUG	594
LPA-4278	UAUCACAGGAAGAACAUGUAA GUCT	195	AGACUUACAUGUUCUCCUGUGAU AGU	595
LPA-4279	AUCACAGGAAGAACAUGUCAG UCTT	196	AAGACUGACAUGUUCUCCUGUGA UAG	596
LPA-4280	UCACAGGAAGAACAUGUCAAU CUTG	197	CAAGAUUGACAUGUUCUCCUGUG AUA	597
LPA-4281	CACAGGAAGAACAUGUCAGAC UUGG	198	CCAAGUCUGACAUGUUCUCCUGU GAU	598
LPA-4282	ACAGGAAGAACAUGUCAGUAU UGGT	199	ACCAAUACUGACAUGUUCUCCUG UGA	599
LPA-4285	GGAAGAACAUGUCAGUCUUAG UCGT	200	ACGACUAAGACUGACAUGUUCUUC CUG	600
LPA-4286	GAAGAACAUGUCAGUCUUGAU CGTC	201	GACGAUCAAGACUGACAUGUUCU CCU	601
LPA-4287	AAGAACAUGUCAGUCUUGGAC GUCT	202	AGACGUCCAAGACUGACAUGUUCU UCC	602
LPA-4288	AGAACAUGUCAGUCUUGGUAG UCTA	203	UAGACUACCAAGACUGACAUGUUC UUC	603
LPA-4325	GGCAUCGGAGGAUCCCAUUAU ACTA	204	UAGUAUAAUGGGAUCCUCCGAUGC CAA	604
LPA-4346	ACUAUCCAAAUGCUGGCCUAA CCAG	205	CUGGUUAGGCCAGCAUUUGGAUAG UAU	605
LPA-4517	GCACAGAGGCUCUUCUGAAC AAGC	206	GCUUGUUCAGAAGGAGCCUCUGUG CUU	606

LPA-4527	UCCUUCUGAACAAGCACCAC UGAG	207	CUCAGUUGGUGCUUGUUCAG AAGG	607
LPA-4528	CCUUCUGAACAAGCACCACAU GAGA	208	UCUCAUGUGGUGCUUGUUCAG AAG	608
LPA-4529	CUUCUGAACAAGCACCACCAG AGAA	209	UUCUCUGGUGGUGCUUGUUCAG AAG	609
LPA-4530	UUCUGAACAAGCACCACCUGA GAAA	210	UUUCUUAGGUGGUGCUUGUUCAG AAG	610
LPA-4531	UCUGAACAAGCACCACCUGAG AAAA	211	UUUUUCAGGUGGUGCUUGUUCAG AAG	611
LPA-4532	CUGAACAAGCACCACCUGAAA AAAG	212	CUUUUUUCAGGUGGUGCUUGUUCAG AAG	612
LPA-4533	UGAACAAGCACCACCUGAGAA AAGC	213	GCUUUUUCAGGUGGUGCUUGUUCAG AAG	613
LPA-4534	GAACAAGCACCACCUGAGAAA AGCC	214	GGCUUUUCAGGUGGUGCUUGUUCAG AAG	614
LPA-4535	AACAAGCACCACCUGAGAAAA GCCC	215	GGGCUUUUCAGGUGGUGCUUGUUCAG AAG	615
LPA-4537	CAAGCACCACCUGAGAAAAAC CCTG	216	CAGGGUUUUUCAGGUGGUGCUUGUUCAG AAG	616
LPA-4538	AAGCACCACCUGAGAAAAAGAC CUGT	217	ACAGGUCUUUUUCAGGUGGUGCUUGUUCAG AAG	617
LPA-4539	AGCACCACCUGAGAAAAAGCAC UGTG	218	CACAGUGCUUUUCAGGUGGUGCUUGUUCAG AAG	618
LPA-4547	CUGAGAAAAGCCCUGUGGUAC AGGA	219	UCCUGUACCACAGGGCUUUUCAG AAG	619
LPA-4556	GCCCUGUGGUCCAGGAUUGAU ACCA	220	UGGUAUCAAUCCUGGACCACAGGG CUU	620
LPA-4559	CUGUGGUCCAGGAUUGCUAAC AUGG	221	CCAUGUUAGCAAUCCUGGACCACAGGG CUU	621
LPA-4611	CUCCACCACUGUCACAGGAAG GACC	222	GGUCCUCCUGUGACAGUGGUGGA GGA	622
LPA-4612	UCCACCACUGUCACAGGAAAG ACCT	223	AGGUCUUUCCUGUGACAGUGGUGGA GGA	623
LPA-4642	UCUUGGUCAUCUAUGAUACAA CACT	224	AGUGUUGUAUCAUAGAUGACCAAG AUU	624
LPA-4643	CUUGGUCAUCUAUGAUACCAC ACTG	225	CAGUGUGGUUAUCAUAGAUGACCAAG AUU	625
LPA-4644	UUGGUCAUCUAUGAUACCAAA CUGG	226	CCAGUUUGGUUAUCAUAGAUGACCAAG AUU	626
LPA-4645	UGGUCAUCUAUGAUACCACAC UGGC	227	GCCAGUGUGGUUAUCAUAGAUGACCAAG AUU	627
LPA-4646	GGUCAUCUAUGAUACCACAAU GGCA	228	UGCCAUGUGGUUAUCAUAGAUGACCAAG AUU	628
LPA-4647	GUCAUCUAUGAUACCACACAG GCAT	229	AUGCCUGUGUGGUUAUCAUAGAUGACCAAG AUU	629
LPA-4648	UCAUCUAUGAUACCACACUAG CATC	230	GAUGCUAGUGUGGUUAUCAUAGAUGACCAAG AUU	630
LPA-4649	CAUCUAUGAUACCACACUGAC AUCA	231	UGAUGUCAGUGUGGUUAUCAUAGAUGACCAAG AUU	631
LPA-4650	AUCUAUGAUACCACACUGGAA UCAG	232	CUGAUUCCAGUGUGGUUAUCAUAGAUGACCAAG AUU	632

LPA-4651	UCUAUGAUACCACACUGGCAU CAGA	233	UCUGAUGCCAGUGUGGUAUCAUAG AUG	633
LPA-4652	CUAUGAUACCACACUGGCAAC AGAG	234	CUCUGUUGCCAGUGUGGUAUCAUA GAU	634
LPA-4655	UGAUACCACACUGGCAUCAA GGAC	235	GUCCUUUGAUGCCAGUGUGGUAUC AUA	635
LPA-4657	AUACCACACUGGCAUCAGAAG ACCC	236	GGGUCUUCUGAUGCCAGUGUGGUA UCA	636
LPA-4673	AGAGGACCCAGAAAACUAAC CAAA	237	UUUGGUUAGUUUCUGGGGUCCUC UGA	637
LPA-4674	GAGGACCCAGAAAACUACAC AAAT	238	AUUUGUGUAGUUUCUGGGGUCCU CUG	638
LPA-4712	AGAACUACUGCAGGAUCCAG AUTC	239	GAAUCUGGAUUCUGCAGUAGUUC UCG	639
LPA-4715	ACUACUGCAGGAUCCAGAAU CUGG	240	CCAGAUUCUGGAUUCUGCAGUAG UUC	640
LPA-4717	UACUGCAGGAUCCAGAUUAU GGGA	241	UCCCAUAAUCUGGAUUCUGCAGU AGU	641
LPA-4718	ACUGCAGGAUCCAGAUUCAG GGAA	242	UUCCUGAAUCUGGAUUCUGCAG UAG	642
LPA-4719	CUGCAGGAUCCAGAUUCUAG GAAA	243	UUUCCUAGAAUCUGGAUUCUGCA GUA	643
LPA-4720	UGCAGGAUCCAGAUUCUGAG AAAC	244	GUUUCUCAGAAUCUGGAUUCUGC AGU	644
LPA-4721	GCAGGAUCCAGAUUCUGGAA AACA	245	UGUUUCCAGAAUCUGGAUUCUG CAG	645
LPA-4724	GGAAUCCAGAUUCUGGGAAAC AACC	246	GGUUGUUUCCAGAAUCUGGAUUC CUG	646
LPA-4738	GGGAAACAACCCUGGUGUUAC ACAA	247	UUGUGUAACACCAGGGUUGUUCC CAG	647
LPA-4739	GGAAACAACCCUGGUGUAAA CAAC	248	GUUGUUUAACACCAGGGUUGUUUC CCA	648
LPA-4771	UGUGUGAGGUGGGAGUACUAC AATC	249	GAUUGUAGUACUCCACCUCACAC ACG	649
LPA-4772	GUGUGAGGUGGGAGUACUGAA AUCT	250	AGAUUUCAGUACUCCACCUCACA CAC	650
LPA-4774	GUGAGGUGGGAGUACUGCAU CUGA	251	UCAGAUUGCAGUACUCCACCUCA CAC	651
LPA-4775	UGAGGUGGGAGUACUGCAAAC UGAC	252	GUCAGUUUGCAGUACUCCACCUC ACA	652
LPA-4795	CUGACACAAUGCUCAGAAAAA GAAT	253	AUUCUUUUCUGAGCAUUGUGUCA GAU	653
LPA-4796	UGACACAAUGCUCAGAAACAG AATC	254	GAUUCUGUUUCUGAGCAUUGUGUC AGA	654
LPA-4797	GACACAAUGCUCAGAAACAAA AUCA	255	UGAUUUUGUUUCUGAGCAUUGUGU CAG	655
LPA-4798	ACACAAUGCUCAGAAACAGAA UCAG	256	CUGAUUCUGUUUCUGAGCAUUGUG UCA	656
LPA-4799	CACAAUGCUCAGAAACAGAAU CAGG	257	CCUGAUUCUGUUUCUGAGCAUUGU GUC	657
LPA-4800	ACAAUGCUCAGAAACAGAAAC AGGT	258	ACCUGUUUCUGUUUCUGAGCAUUG UGU	658

LPA-4801	CAAUGCUCAGAAACAGAAUAA GGTG	259	CACCUUAUUCUGUUUCUGAGCAU GUG	659
LPA-4802	AAUGCUCAGAAACAGAAUCAG GUGT	260	ACACCUGAUUCUGUUUCUGAGCAU UGU	660
LPA-4803	AUGCUCAGAAACAGAAUCAAG UGTC	261	GACACUUGAUUCUGUUUCUGAGCA UUG	661
LPA-4804	UGCUCAGAAACAGAAUCAGAU GUCC	262	GGACAUCUGAUUCUGUUUCUGAGC AUU	662
LPA-4806	CUCAGAAACAGAAUCAGGUAU CCTA	263	UAGGAUACCUGAUUCUGUUUCUGA GCA	663
LPA-4808	CAGAAACAGAAUCAGGUGUAC UAGA	264	UCUAGUACACCUGAUUCUGUUUCU GAG	664
LPA-4809	AGAAACAGAAUCAGGUGUCAU AGAG	265	CUCUAUGACACCUGAUUCUGUUUC UGA	665
LPA-4810	GAAACAGAAUCAGGUGUCCAA GAGA	266	UCUCUUGGACACCUGAUUCUGUUU CUG	666
LPA-4811	AAACAGAAUCAGGUGUCCUAG AGAC	267	GUCUCUAGGACACCUGAUUCUGUU UCU	667
LPA-4812	AACAGAAUCAGGUGUCCUAAA GACT	268	AGUCUUUAGGACACCUGAUUCUGU UUC	668
LPA-4814	CAGAAUCAGGUGUCCUAGAAA CUCC	269	GGAGUUUCUAGGACACCUGAUUCU GUU	669
LPA-4816	GAAUCAGGUGUCCUAGAGAAU CCCA	270	UGGGAUUCUCUAGGACACCUGAUU CUG	670
LPA-4818	AUCAGGUGUCCUAGAGACUAC CACT	271	AGUGGUAGUCUCUAGGACACCUGA UUC	671
LPA-4822	GGUGUCCUAGAGACUCCCAAU GUTG	272	CAACAUUGGGAGUCUCUAGGACAC CUG	672
LPA-4827	CCUAGAGACUCCACUGUUAU UCCA	273	UGGAAUAACAGUGGGAGUCUCUAG GAC	673
LPA-4828	CUAGAGACUCCACUGUUGAU CCAG	274	CUGGAUCAACAGUGGGAGUCUCUA GGA	674
LPA-4829	UAGAGACUCCACUGUUGUAC CAGT	275	ACUGGUACAACAGUGGGAGUCUCU AGG	675
LPA-4830	AGAGACUCCACUGUUGUUAC AGTT	276	AACUGUAACAACAGUGGGAGUCUC UAG	676
LPA-4831	GAGACUCCACUGUUGUCAA GUTC	277	GAACUUGAACAACAGUGGGAGUCU CUA	677
LPA-4832	AGACUCCACUGUUGUCCAG UUC	278	GGAACUGGAACAACAGUGGGAGUC UCU	678
LPA-4867	GCUCAUUCUGAAGCAGCACAA ACTG	279	CAGUUUGUGCUGCUUCAGAAUGAG CCU	679
LPA-4868	CUCAUUCUGAAGCAGCACCAA CUGA	280	UCAGUUGGUGCUGCUUCAGAAUGA GCC	680
LPA-4869	UCAUUCUGAAGCAGCACCAAC UGAG	281	CUCAGUUGGUGCUGCUUCAGAAUG AGC	681
LPA-4870	CAUUCUGAAGCAGCACCAAU GAGC	282	GCUCAUUGGUGCUGCUUCAGAAU GAG	682
LPA-4871	AUUCUGAAGCAGCACCAACAG AGCA	283	UGCUCUGUUGGUGCUGCUUCAGAA UGA	683
LPA-4872	UUCUGAAGCAGCACCAACUAA GCAA	284	UUGC UUAGUUGGUGCUGCUUCAGA AUG	684

LPA-4873	UCUGAAGCAGCACCAACUGAG CAAA	285	UUUGCUCAGUUGGUGCUGCUUCAG AAU	685
LPA-4874	CUGAAGCAGCACCAACUGAAC AAAC	286	GUUUGUUCAGUUGGUGCUGCUUCA GAA	686
LPA-4875	UGAAGCAGCACCAACUGAGAA AACC	287	GGUUUUCUCAGUUGGUGCUGCUUC AGA	687
LPA-4876	GAAGCAGCACCAACUGAGCAA ACCC	288	GGGUUUGCUCAGUUGGUGCUGCUU CAG	688
LPA-4877	AAGCAGCACCAACUGAGCAAA CCCC	289	GGGGUUUGCUCAGUUGGUGCUGCU UCA	689
LPA-4912	CAGUGCUACCAUGGUAAUGAC CAGA	290	UCUGGUCAUUACCAUGGUAGCACU GCC	690
LPA-4913	AGUGCUACCAUGGUAAUGGAC AGAG	291	CUCUGUCCAUAUACCAUGGUAGCAC UGC	691
LPA-4948	ACAUUCUCCACCACUGUCAAA GGAA	292	UCCUUUGACAGUGGUGGAGAAUG UGC	692
LPA-4959	CACUGUCACAGGAAGGACAAG UCAA	293	UUGACUUGUCCUCCUGUGACAGU GGU	693
LPA-4960	ACUGUCACAGGAAGGACAUAU CAAT	294	AUUGAUAUGUCCUCCUGUGACAG UGG	694
LPA-4961	CUGUCACAGGAAGGACAUGAC AATC	295	GAUUGUCAUGUCCUCCUGUGACA GUG	695
LPA-4962	UGUCACAGGAAGGACAUGUAA AUCT	296	AGAUUUACAUGUCCUCCUGUGAC AGU	696
LPA-4963	GUCACAGGAAGGACAUGUCAA UCTT	297	AAGAUUGACAUGUCCUCCUGUGA CAG	697
LPA-4964	UCACAGGAAGGACAUGUCAAU CUTG	298	CAAGAUUGACAUGUCCUCCUGUG ACA	698
LPA-4966	ACAGGAAGGACAUGUCAUAU UGGT	299	ACCAAUAUUGACAUGUCCUCCUG UGA	699
LPA-4967	CAGGAAGGACAUGUCAUAU GGTC	300	GACCAUGAUUGACAUGUCCUCCU GUG	700
LPA-4968	AGGAAGGACAUGUCAAUUCUAG GUCA	301	UGACCUAGAUUGACAUGUCCUCC UGU	701
LPA-4969	GGAAGGACAUGUCAAUUCUAG UCAT	302	AUGACUAAGAUUGACAUGUCCUUC CUG	702
LPA-4970	GAAGGACAUGUCAAUUCUUGAU CATC	303	GAUGAUCAAGAUUGACAUGUCCU CCU	703
LPA-4971	AAGGACAUGUCAAUUCUUGGAC AUCC	304	GGAUGUCCAAGAUUGACAUGUCCU UCC	704
LPA-4972	AGGACAUGUCAAUUCUUGGUAA UCCA	305	UGGAUUACCAAGAUUGACAUGUCC UUC	705
LPA-4973	GGACAUGUCAAUUCUUGGUCAU CCAT	306	AUGGAUGACCAAGAUUGACAUGUC CUU	706
LPA-4974	GACAUGUCAAUUCUUGGUCAAC CATG	307	CAUGGUUGACCAAGAUUGACAUGU CCU	707
LPA-4975	ACAUGUCAAUUCUUGGUCAUAC AUGA	308	UCAUGUAUGACCAAGAUUGACAUG UCC	708
LPA-4976	CAUGUCAAUUCUUGGUCAUCAA UGAC	309	GUCAUUGAUGACCAAGAUUGACA GUC	709
LPA-4977	AUGUCAAUUCUUGGUCAUCCAU GACA	310	UGUCAUGGAUGACCAAGAUUGACA UGU	710

LPA-4978	UGUCAAUUCUUGGUCAUCCAAG ACAC	311	GUGUCUUGGAUGACCAAGAUUGAC AUG	711
LPA-4979	GUCAAUCUUGGUCAUCCAUA CACC	312	GGUGUUAUGGAUGACCAAGAUUGA CAU	712
LPA-4980	UCAAUUCUUGGUCAUCCAUGAC ACCA	313	UGGUGUCAUGGAUGACCAAGAUUG ACA	713
LPA-4981	CAAUCUUGGUCAUCCAUGAAA CCAC	314	GUGGUUUCUUGGAUGACCAAGAUU GAC	714
LPA-4982	AAUCUUGGUCAUCCAUGACAC CACA	315	UGUGGUGUCAUGGAUGACCAAGAU UGA	715
LPA-4983	AUCUUGGUCAUCCAUGACAAC ACAC	316	GUGUGUUGUCAUGGAUGACCAAGA UUG	716
LPA-5048	UGACAAUGAACUACUGCAGAA AUCC	317	GGAUUUCUGCAGUAGUUCAUUGUC AGG	717
LPA-5049	GACAAUGAACUACUGCAGGAA UCCA	318	UGGAUUCUGCAGUAGUUCAUUGU CAG	718
LPA-5050	ACAAUGAACUACUGCAGGAAU CCAG	319	CUGGAUUCUGCAGUAGUUCAUUG UCA	719
LPA-5051	CAAUGAACUACUGCAGGAAAC CAGA	320	UCUGGUUUCUGCAGUAGUUCAU GUC	720
LPA-5052	AAUGAACUACUGCAGGAAUAC AGAT	321	AUCUGUAUUCUGCAGUAGUUCAU UGU	721
LPA-5053	AUGAACUACUGCAGGAAUCAA GATG	322	CAUCUUGAUUUCUGCAGUAGUUCA UUG	722
LPA-5054	UGAACUACUGCAGGAAUCCAG AUGC	323	GCAUCUGGAUUCUGCAGUAGUUC AUU	723
LPA-5058	CUACUGCAGGAAUCCAGAUAC CGAT	324	AUCGGUAUCUGGAUUCUGCAGUA GUU	724
LPA-5084	CAGGCCCUGGUGUUUUACAA UGGA	325	UCCAUUGUAAAACACCAAGGGCCU GUA	725
LPA-5090	CUUGGUGUUUUACCAUGGAAC CCAG	326	CUGGGUCCAUGGUAAAACACCAA GGG	726
LPA-5091	UUGGUGUUUUACCAUGGACAC CAGC	327	GCUGGUGUCCAUGGUAAAACACCA AGG	727
LPA-5092	UGGUGUUUUACCAUGGACCAC AGCA	328	UGCUGUGGUCCAUGGUAAAACACC AAG	728
LPA-5093	GGUGUUUUACCAUGGACCCAA GCAT	329	AUGCUUGGGUCCAUGGUAAAACAC CAA	729
LPA-5094	GUGUUUUACCAUGGACCCACAG CATC	330	GAUGCUGGGGUCCAUGGUAAAACA CCA	730
LPA-5096	GUUUUACCAUGGACCCACAGAA UCAG	331	CUGAUUCUGGGGUCCAUGGUAAAA CAC	731
LPA-5124	GGAGUACUGCAACCUGACGAG AUGC	332	GCAUCUCGUCAGGUUGCAGUACUC CCA	732
LPA-5125	GAGUACUGCAACCUGACGCAA UGCT	333	AGCAUUGCGUCAGGUUGCAGUACU CCC	733
LPA-5127	GUACUGCAACCUGACGCGAAG CUCA	334	UGAGCUUCGCGUCAGGUUGCAGUA CUC	734
LPA-5128	UACUGCAACCUGACGCGAUAC UCAG	335	CUGAGUAUCGCGUCAGGUUGCAGU ACU	735
LPA-5131	UGCAACCUGACGCGAUGCUGAA GACA	336	UGUCUUAGCAUCGCGUCAGGUUGC AGU	736

LPA-5136	CCUGACGCGAUGCUCAGACAC AGAA	337	UUCUGUGUCUGAGCAUCGCGUCAG GUU	737
LPA-5137	CUGACGCGAUGCUCAGACAAA GAAG	338	CUUCUUUGUCUGAGCAUCGCGUCA GGU	738
LPA-5144	GAUGCUCAGACACAGAAGGAA CUGT	339	ACAGUCCUUCUGUGUCUGAGCAU CGC	739
LPA-5145	AUGCUCAGACACAGAAGGGAC UGTG	340	CACAGUCCUUCUGUGUCUGAGCA UCG	740
LPA-5151	AGACACAGAAGGGACUGUGAU CGCT	341	AGCGAUCACAGUCCUUCUGUGUC UGA	741
LPA-5467	GCAUCCUCUUCAUUUUGAUUUAU GGGA	342	UCCCAUAAUCAAUGAAGAGGAUG CAC	742
LPA-5468	CAUCCUCUUCAUUUUGAUUGAG GGAA	343	UUCCCUCAAUCAAUGAAGAGGAU GCA	743
LPA-5469	AUCCUCUUCAUUUUGAUUGUAG GAAG	344	CUUCCUACAAUCAAUGAAGAGGA UGC	744
LPA-5470	UCCUCUUCAUUUUGAUUGUGAG AAGC	345	GCUUCUCACAAUCAAUGAAGAGG AUG	745
LPA-5471	CCUCUUCAUUUUGAUUGGGAA AGCC	346	GGCUUCCACAAUCAAUGAAGAG GAU	746
LPA-5474	CUUCAUUUGAUUGUGGGAAAC CUCA	347	UGAGGUUCCACAAUCAAUGAA GAG	747
LPA-5475	UUCAUUUGAUUGUGGGAAAGAC UCAA	348	UUGAGUCUCCACAAUCAAUGA AGA	748
LPA-5476	UCAUUUGAUUGUGGGAAAGCAU CAAG	349	CUUGAUGCUUCCACAAUCAAUG AAG	749
LPA-5477	CAUUUGAUUGUGGGAAAGCCAC AAGT	350	ACUUGUGGCUUCCACAAUCAAU GAA	750
LPA-5478	AUUUGAUUGUGGGAAAGCCUAA AGTG	351	CACUUUAGGCUUCCACAAUCAA UGA	751
LPA-5486	GUGGGAAGCCUCAAGUGGAAC CGAA	352	UUCGGUCCACUUGAGGCUUCCCA CAA	752
LPA-5509	AAGAAAUGUCCUGGAAGCAAU GUAG	353	CUACAUUGCUCUCCAGGACAUUUCU UCG	753
LPA-5510	AGAAAUGUCCUGGAAGCAUAG UAGG	354	CCUACUAGCUUCCAGGACAUUUC UUC	754
LPA-5511	GAAAUGUCCUGGAAGCAUUUAU AGGG	355	CCCUAUAUAGCUUCCAGGACAUUU CUU	755
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LPA-5514	AUGUCCUGGAAGCAUUGUAAG GGGG	357	CCCCCUACAAUGCUUCCAGGACA UUU	757
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LPA-5585	CAAGGUUUGGAAAGCACUUUAU GUGG	362	CCACAUAAUGUCUUCCAAACCUU GUU	762

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LPA-5592	UGGAAAGCACUUCUGUGGAAG CACC	365	GGUGCUUCCACAGAAGUGCUUUC AAA	765
LPA-5606	GUGGAGGCACCUUAAUAUCAC CAGA	366	UCUGGUGAUUUAAGGUGCCUCCA CAG	766
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LPA-5902	GAAACCCAAGGUACCUUUGAG ACTG	387	CAGUCUCAAGGUACCUUGGGUUU CUC	787
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Human (Hs): NM 005577.3 (SEQ ID NO: 1)			
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Cynomolgus monkey (Mf): XM 015448517.1 (SEQ ID NO: 2)					
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GGCACATTCT	CCACCACTAT	CACAGGAAGA	ACATGTCAGT	CTTGGTTGTC	TATGACACCA
CATCGGCATC	GGAGGATCCC	ATTACGCTAT	CCAAATGCTG	GCCTGACCAG	GAACCTATTGC
AGAAATCCAG	ATGCTGAGAT	TCGCCCTTGG	TGTTACACCA	TGGATCCCAG	TGTCAGGTGG
GAGTACTGCA	ACCTGACACA	ATGTCCAGTG	ACAGAATCAA	GTGTCCTCAC	AACTCCACAG
TGTTCCCGG	TTCCAAGCAC	AGAGGCTCCT	TCTGAACAAG	CACCACCTGA	GAAAAGCCCT
GTGGTCCAGG	ATTGCTACCA	TGGTGATGGA	CAGAGTTATC	GAGGCACATC	CTCCACCACT
GTACACAGGAA	GGAAC TGTC	GTCTTGGTCA	TCTATGATAC	CACACTGGCA	TCAGAGGACC
CCAGAAAACCT	ACCCAAATGC	TGGCCTGACC	AGGAAC TACT	GCAGGAATCC	AGATTCTGGG
AAACAACCCCT	GGTGT TACAC	GACTGATCCA	TGTGTGAGGT	GGGAGTACTG	CAACCTGACA
CAATGCTCAG	AAACAGAATC	AGGTGTCCTA	GAGACTCCCA	CTGTGT TCC	GGTTCCAAGC
ATGGAAGCTC	ATTCTGAAGC	AGCACCAACT	GAGCAAAC TC	CTGTGGTCCA	GCAGTGCTAC
CATGGTAATG	GACAGAGTTA	TCGAGGCACA	TTCTCCACCA	CTGT CACAGG	AAGGACATGT
CAATCTTGGT	CATCCATGAC	ACCACACCAG	CATAAGAGGA	CCCCGAAAA	CCACCCAAAT
GATGACTTGA	CAATGAAC TA	CTGCAGGAAT	CCAGATGCTG	ACACAGGCC	TTGGTGT TTT
ACCATGGACC	CCAGCGTCAG	GCGGGAGTAC	TGCAACCTGA	CGCGATGCTC	AGACACAGAA
GGGACTGTGG	TCACACCTCC	GACTGTTATC	CCGGTTCCAA	GCCTAGAGGC	TCCTTCTGAA
CAAGCATCCT	CTTCATTTGA	TTGTGGGAAG	CCTCAAGTGG	AGCCAAAGAA	ATGTCTGGA
AGCATTTGTA	GTGGGTGTGT	GGCCCCACCA	CATTCTTGGC	CCTGGCAAGT	CAGTCTTAGA
ACAAGTTTGG	GAAAGCACTT	CTGTGGAGGC	ACCTTAATAT	CCCCAGAGTG	GGTGCTGACT
GCTGCTTGCT	GCTTGGAGAC	GTTCTCAAGG	CCTTCCTTCT	ACAAGGTCAT	CCTGGGTGCA
CACCAAGAAG	TGAATCTCGA	ATCTCACGTT	CAAGAAATAG	AAGTGTCTAG	GTTGT TCTTG
GAGCCCATAG	GAGCAGATAT	TGCCTTGCTA	AAGCTAAGCA	GGCCTGCCAT	CATCACTGAC
AAAGTAATCC	CAGCCTGTCT	GCCGTCTCCA	AATTACGTGA	TCACCGTCTG	GACTGAATGT
TACATCACTG	GCTGGGGAGA	AACCCAAGGT	ACCTTTGGGG	CTGGCCTTCT	CAAGGAAGCC
CAGCTTCATG	TGATTGAGAA	TACAGTGTGC	AATCACTACG	AGTTTCTGAA	TGGAAGAGTC
AAATCCACCG	AGCTCTGTGC	TGGGCATTTG	GCCGGAGGCA	CTGACAGATG	CCAGGGTGAC
AGTGGAGGGC	CTGTGGTTTG	CTTCGACAAG	GACAAATACA	TTTTACGAGG	AATAACTTCT
TGGGGTCCTG	GCTGTGCATG	CCCCAATAAG	CCTGGTGTCT	ATGTTCTGTG	TTCAAGCTTT
GTCACTTGGA	TTGAGGGAGT	GATGAGAAAT	AATTAATTGA	ACAAGAGACA	GAGTGAAGCA
TTGACTCACC	TAGAGGCTAG	AATGGGGGTA	GGGATTTAGC	ACGCTGGAAA	TAACGGACAG
TAATCAAACG	AAGACACTGT	CCCCAGCTAC	CAACTATGCC	AAACCTCAGC	ATTTT TGGTA
TTATTGTGTA	TAAGCTTTTC	CCGTCTGACT	GCTGGGTTCT	CCAATAAGGT	GACATAGCTA
TGCCATTTGT	TAAAAATAAA	CTCTGTACTT	ATTTTGATTT	GAGTAAA	
Rhesus monkey: XM 028847001.1 (SEQ ID NO: 3)					
AGCCTTGCCCT	TTGAAATGTT	CCAGTTGGAA	CATTGCTGGG	CAGCGTGCAA	ACAGGAGCGA
ACGTGAGCCG	GGGCGGCAGG	GGGCAGCAGA	CCCCACACTT	TGTCCATGCC	TCAGGTGGGA
GGAAGTGTCC	GGCTCCAGAA	ACCTGCCGCG	GGCTTTATCC	CAAGCGACTT	CAGCCAGCAG
ACGGTTCATG	TCCTGAGGCT	GCAAAAATACG	AGTTCTGCCA	TCATCGCTGA	CAAAGTCATC
CCAGTTTGTG	TGCCATCCCC	AAATTATGCG	ATCGCCAACC	AGACTGAATG	TTATGTCACT
GGCTGGGGAG	AAACCCAAGC	ACTACCTGAG	CAAAGCCATG	TGGTCCAGGA	TTGCTACCAT
GGTGATGGAC	AGAGTTATCA	AGGCACATCC	TCCACCACTG	TCACAGGAAG	GACCTGCCAA

GCTTGGTCAT	CTATGGAACC	ACATCAGCAT	AATAGAACCA	CAGAAAACCTA	CCCAATGCT
GGCTTGATCA	GGAACTACTG	CAGGAATCCA	GATCCTGTGG	CAGCCCCTTA	TTGTTATACG
ATGGATCCCA	ATGTCAGGTG	GGAGTACTGC	AACCTGACAC	AATGCTCAGA	CGCAGAAGGG
ACTGCCGTCG	CACCTCCGAA	TGTCACCCCG	GTCCAAGCC	TAGAGGCTCT	TTCCGAACAA
GCACCGACTG	AGCAAAGGCC	TGGGGTGCAG	GAGTGCTACC	ACGGTAATGG	ACAGAGTTAT
CGAGGCACAT	ACTTCACCAC	TGTGACAGGA	AGAACCTGCC	AAGCTTGGTC	ATCTATGACA
CCACATTCCT	ATAGTCGTAC	CCCAGAAAAC	TACCCAAATG	GTGGCTTGAT	CAGGAACCTAC
TGCAGGAATC	CAGATCCTGT	GGCAGCCCCT	TATTGTTATA	CCATGGATCC	CAATGTCAGG
TGGGAGTACT	GCAACCTGAC	ACAATGCTCA	GACGCAGAAG	GGACTGCCGT	CGCACCTCCG
AATGTCACCC	CGGTTCCAAG	CCTAGAGGCT	CCTTCCGAAC	AAGCACCAC	TGAGCAAAGG
CCTGGGGTGC	AGGAGTGCTA	CCACGGTAAT	GGACAGAGTT	ATCGAGGCAC	ATACTTCACC
ACTGTGACAG	GAAGAACCTG	CCAAGCTTGG	TCATCTATGA	CACCACATTC	TCATAGTCTG
ACCCAGAAAA	ACTACCCAAA	TGGTGGCTTG	ATCAGGAACT	ACTGCAGGAA	TCCAGATCCT
GTGGCAGCCC	CTTATTGTTA	TACCATGGAT	CCCAATGTCA	GGTGGGAGTA	CTGCACCTG
ACACAATGCT	CAGACGCAGA	GGGGACTGCC	GTGCGACCTC	CGACTGTGAC	CCCGGTTCCA
AGCCTAGAGT	TCTCTTCTGA	GCAAGCACCG	ACTGAGCAAA	GGCCTGGGGT	GCAGGAGTGC
TACCACGGTA	ATGGACAGAG	TTATCGAGGC	ACATACTTCA	CCACTGTGAC	AGGAAGAACC
TGCCAAGCTT	GGTCATCTAT	GACACCGCAC	TCTCATAGTC	GGACCCCGGA	AAACTACCCA
AATGTTGGCT	TGATCAGGAA	CTACTGCAGG	AATCCAGATC	CTGTGGCAGC	CCCTTATTGT
TATACGATGG	ATCCCAATGT	CAGGTGGGAG	TACTGCAACC	TGACACAATG	CTCAGACGCA
GAAGGGACTG	CCGTGCGACC	TCCGAATGTC	ACCCCGGTTT	CAAGCCTAGA	GGTCTCTTCC
GAACAAGCAC	CGACTGAGCA	AAGGCCTGGG	GTGCAGGAGT	GCTACCACGG	TAATGGACAG
AGTTATCGAG	GCACATACTT	CACCACTGTG	ACAGGAAGAA	CCTGCCAAGC	TTGGTCATCT
ATGACACCGC	ACTCTCATAG	TCGGACCCCG	GAAAACTACC	CAAATGGTGG	CTTGATCAGG
AACTATGCA	GGAAATCCAGA	TCCTGTGGCA	GCCCCCTATT	GTTATACGAT	GGATCCCAAT
GTCAGGTGGG	TGACTGCAA	CTGACACAA	TGCTCAGACG	CAGAAGGGAC	TGCCGTGCGA
CCTCCGAATG	TCACCCCGGT	TCCAAGCCTA	GAGGCTCCTT	CCGAACAAGC	ACCAACTGAG
CAAAGGCCTG	GGNTGCAAGG	GTGCTACCAT	GGTAATGGAC	AGAGTTATCG	AGGCACATAC
TTCAACCACTG	TGACAGGAAG	AACCTGCCAA	GCTTGGTTCAT	CTATGACACC	GCACTCTCAT
AGTCGGACCC	CGGAAAACCTA	CCCAAATGGT	GGCTTGATCA	GGAACCTACTG	CAGGAATCCA
GATCCTGTGG	CAGCCCCTTA	TTGTTATACC	ATGGATCCCA	ATGTCAGGTG	GNAGTACTGC
AACCTGACAC	AATGCTCAGA	CGCAGAAGGG	ACTGCCGTCG	CACCTCCGAC	TGTCACCCCG
GTTCGAAGCC	TAGAGGCTCC	TTTCGAGCAAG	GCACCGACTG	AGCAAAGGCC	TGGGNTGACG
GAGTGCTACC	ACGGTAATGG	ACAGAGTTAT	CGAGGCACAT	ACTTCACCAC	TGTGACAGGA
AGAAGCTGCC	AAGCTTGGTC	ATCTATGACA	CCGCACTCTC	ATAGTCGGAC	CCCGGAAAAC
TACCCAAATG	GTGGCTTGAT	CAGGAACCTAC	TGCAGGAATC	CAGATCCTGT	GGCAGCCCCT
TATTGTTATA	CGATGGATCC	CAATGTCAGG	TGGGAGTACT	GCAACCTGAC	ACAATGCTCA
GACGCAGAAG	GGACTGCCGT	CGCACCTCCG	AATGTCACCC	CGGTTCCAAG	CCTAGAGGCT
CCTTCCGAAC	AAGCACCGAC	TGAGCAAAGG	CCTGGGGTGC	AGGAGTGCTA	CCACGGTAAT
GGACAGAGTT	ATCGAGGCAC	ATACTTCACC	ACTGTGACAG	GAAGAACCCTG	CCAAGCTTGG
TCATCTATGA	CACCGCACTC	TCATAGTCGG	ACCCCGGAAA	ACTACCCAAA	TGGTGGCTTG
ATCAGGAACT	ACTGCAGGAA	TCCAGATCCT	GTGGCAGCCC	CTTATTGTTA	TACCATGGAT
CCCAATGTCA	GGTGGGAGTA	CTGCAACCTG	ACACAATGCT	CAGACGCAGA	AGGGACTGCC
GTGCGACCTC	CGAATGTCAC	CCCGGTTCCA	AGCCTAGAGG	CTCCTTCTGA	GCAAGCACCA
ACTGAGCAAA	GGCTTGGGGT	GCAGGAGTGC	TACCACAGTA	ATGGACAGAG	TTATCGAGGC
ACATACTTCA	CCACTGTGAC	AGGAAGAACC	TGCCAAGCTT	GGTCATCTAT	GACACCACAC
TCTCATAGTC	GGACCCGAGA	AAACTACCCA	AATGCTGGCT	TGGTCAAGAA	CTACTGCCGA
AATCCAGATC	CTGTGGCAGC	CCCTTGGTGT	TATACAACGG	ATCCCAAGTGT	CAGGTGGGAG
TACTGCAACC	TGACACGATG	CTCAGATGCA	GAAGGGACTG	CTGTGATGCC	TCCAATATT
ATTCGGGTTT	CAAGCCTAGA	GGCTTTTCTT	GAACAAGAAC	CTACTGAGGA	AACCCCGGGG
GTACAGGAGT	GCTACTACCA	TTATGGACAG	AGTTATCGAG	GCACATACTC	CACCACTGTT
ACAGGAAGAA	CTTGCCAAGC	TTGGTCACTT	ATGACACCAC	ACCAGCATAG	TCCGACCCCA
AAAAACTATC	CAAAATGCTGG	CCTGACCAGG	AACTACTGCA	GGAATCCAGA	TGCTGAGATT
CGCCCTTGGT	GTTATACCAT	GGATCCCAGT	GTGAGGTGGG	AGTACTGCAA	CCTGACACAA
TGTCTGGTGA	CAGAATCAAG	TGTCTTGAA	ACTCTCACAG	TGGTCCGAGA	TCCAAGCACA
CAGGCTTCTT	CTGAAGAAGC	ACCAACGGAG	CAAAGTCCCG	AGGTCCAGGA	CTGCTACCAT
GGTGATGGAC	AGAGTTATCG	AGGCTCATTC	TCCACCACCTG	TCACAGGAAG	GACATGTCAG
TCTTGGTCCT	CTATGACACC	ACACTGGCAT	CAGAGGACAA	CAGAATATTA	TCCAGATGGT
GGCCTGACCA	GGAACCTACTG	CAGGAATCCA	GATGCTGAGA	TTCCGCCCTTG	GTGTTATACC
ATGGATCCCA	GTGTCAGGTG	GGAGTACTGC	AACCTGACAC	AATGTCCAGT	GACAGAATCA
AGTGTCTCTG	CAACGTCCAT	GGCTGTTTCT	GAACAAGCAC	CAATGGAGCA	AAGCCCCGGG

GTCCAGGACT	GCTACCATGG	TGATGGACAG	AGTTATCGAG	GTTCATTCTC	CACCACTGTC
ACAGGAAGGA	CATGTCAGTC	TTGGTCCTCT	ATGACACCAC	ACTGGCATCA	GAGGACCATA
GAATACTACC	CAAAATGGTGG	CCTGACCAAG	AACTACTGCA	GGAATCCAGA	TGCTGAGATT
CGCCCTTGGT	GTTATACCAT	GGATCCCAGA	GTCAGATGGG	AGTACTGCAA	CCTGACACAA
TGTGTGGTGA	TGGAATCAAG	TGTCCTTGCA	ACTCCCATGG	TGGTCCCAGT	TCCAAGCAGA
GAGGTTCCCT	CTGAAGAAGC	ACCAACTGAA	AACAGCCCTG	GGGTCCAGGA	CTGTACCAA
GGTGATGGAC	AGAGTTATCG	AGGCACATTC	TCCACCACTA	TCACAGGAAG	AACATGTCAG
TCTTGGTGTG	CTATGACACC	ACATCGGCAT	CGGAGGATCC	CATTACGCTA	TCCAAATGCT
GGCCTGACCA	GGAACATATT	CAGAAATCCA	GATGCTGAGA	TTCGCCCTTG	GTGTTACACC
ATGGATCCCA	GTGTCAGGTG	GGAGTACTGC	AACCTGACAC	AATGTCCAGT	GACAGAATCA
AGTGTCTCTA	CAACTCCAC	GGTGGTCCCG	GTTCCAAGCA	CAGAGGCTCC	TTCTGAACAA
GCACCACCTG	AGAAAAAGCCC	TGTGGTCCAG	GATTGCTACC	ATGGTGATGG	ACAGAGTTAT
CGAGGCACAT	CCTCCACCAC	TGTCACAGGA	AGGAACTGTC	AATCTTGGTC	ATCTATGATA
CCACACTGGC	ATCAGAGGAC	CCCAGAAAAC	TACCCAAATG	CTGGCCTGAC	CAGGAACTAC
TGCAGGAATC	CAGATTCTGG	GAACAACCC	TGGTGTTACA	CGACTGATCC	ATGTGTGAGG
TGGGAGTACT	GCAACCTGAC	ACAATGCTCA	GAACAGAAAT	CAGGTGTCTT	AGAGACTCCC
ACTGTTGTTC	CGGTTCCAAG	CATGGAAGCT	CATTCTGAAG	CAGCACCAC	TGAGCAAACC
CCTGTGGTCC	AGCAGTGCTA	CCATGGTAAT	GGACAGAGTT	ATCGAGGCAC	ATTCTCCACC
ACTGTCACAG	GAAGGACATG	TCAATCTTGG	TCATCCATGA	CACCACACCA	GCATAGAGG
ACCCCGGAAA	ACCACCCAAA	TGATGACTTG	ACAATGAACT	ACTGCAGGAA	TCCAGATGCT
GACACAGGCC	CTTGGTGTTC	TACCATGGAC	CCCAGCGTCA	GGCGGGAGTA	CTGCAACCTG
ACGCGATGCT	CAGACACAGA	AGGGACTGTG	GTCACACCTC	CGACTGTTAT	CCCGGTTCCA
AGCCTAGAGG	CTCCTTCTGA	ACAAGCATCC	TCTTCATTTG	ATTGTGGGAA	GCCTCAAGTG
GAGCCAAAGA	AATGTCTTGG	AAGCATTTGA	GGTGGGTGTG	TGGCCACCC	ACATTCCTTG
CCCTGGCAAG	TCAGTCTTAG	AACAAGGTTT	GAAAGCACT	TCTGTGGAGG	CACCTTAATA
TCCCCAGAGT	GGGTGCTGAC	TGCTGCTTGC	TGCTTGAGAA	CGTTCTCAAG	GCCTTCCTTC
TACAAGGTCA	TCCTGGGTGC	ACACCAAGAA	GTGAATCTCG	AATCTCATGT	TCAAGAAATA
GAAGTGTCTA	GGTTGTTCCT	GGAGCCCATA	GGAGCAGATA	TTGCCTTGCT	AAAGCTAAGC
AGGCCTGCCA	TCATCACTGA	CAAAGTAATC	CCAGCCTGTC	TGCCGTCTCC	AAATTACGTG
ATCACCGCCT	GGACTGAATG	TTACATCACT	GGCTGGGGAG	AAACCCAAGG	TACCTTTGGG
GCTGGCCTTC	TCAAGGAAGC	CCAGCTTCAT	GTGATTGAGA	ATACAGTGTG	CAATCACTAC
GAGTTTCTGA	ATGGAAGAGT	CAAATCCACT	GAGTCTGTG	CTGGGCATTT	GGCCGGAGGC
ACTGACAGAT	GCCAGGGTGA	CAATGGAGGG	CCTGTGGTTT	GCTTCGACAA	GGACAAATAC
ATTTTACGAG	GAATAACTTC	TTGGGGTCCT	GGCTGTGCAT	GCCCCAATAA	GCCTGGTGTC
TATGTTCTGTG	TTTCAAGCTT	TGTCACCTGG	ATTGAGGGAG	TGATGAGAAA	TAATTAATTG
AACAAGAGAC	AGAGTGAAGC	ATTGACTCAC	CTAGAGGCTA	GAATGGGGGT	AGGGATTTAG
CACGCTGGAA	ATAACGGACA	GTAATCAAAC	GAAGACACTG	TCCCCAGCTA	CCAACTATGC
CAAACCTCAG	CATTTTGGT	ATTATTGTGT	ATAAGCTTTT	CCTGTCTGAC	TGCTGGGTTT
TCCAATAAGG	TGACATAGCT	ATGCCATTTC	TTAAAAATAA	ACTCTGTACT	TATTTTGATT
TGAGTAAA					

Table 6. *LPA* Oligonucleotide Sequences (modified)

Oligonucleotide	Sequence (Sense Strand)	SEQ ID NO:	Sequence (Antisense Strand)	SEQ ID NO:
LPA-0190-M1	[mUs] [mC] [mC] [mA] [mC] [mC] [mA] [fC] [fU] [fG] [fU] [mC] [mA] [mC] [mA] [mG] [mG] [mA] [mA] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA-GalNAc] [ademA-GalNAc] [ademA-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	388	[MePhosphonate-40-mUs] [fUs] [fUs] [fC] [fC] [mU] [fG] [mU] [mG] [fA] [mC] [mA] [mG] [fU] [mG] [mG] [mU] [mG] [mG] [mAs] [mGs] [mG]	788
LPA-0501-M1	[mUs] [mG] [mG] [mU] [mA] [mA] [mU] [fG] [fG] [fA] [fA]	389	[MePhosphonate-40-mUs] [fAs] [fUs] [fA] [fA] [mU]	789

	fC] [mA] [mG] [mA] [mG] [mU] [mU] [mA] [mU] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [adema-GalNAc] [adema-GalNAc] [adema-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]		C] [fU] [mC] [mU] [fG] [mU] [mC] [mC] [fA] [mU] [mU] [mA] [mC] [mC] [mAs] [mGs] [mG]	
LPA-3100-M1	[mUs] [mA] [mC] [mU] [mG] [mC] [mA] [fA] [fC] [fC] [fU] [mG] [mA] [mC] [mA] [mC] [mG] [mA] [mU] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [adema-GalNAc] [adema-GalNAc] [adema-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	390	[MePhosphonate-40-mUs] [fAs] [fUs] [fC] [fG] [mU] [fG] [mU] [mC] [fA] [mG] [mG] [mU] [fU] [mG] [mC] [mA] [mG] [mU] [mAs] [mGs] [mG]	790
LPA-3286-M1	[mAs] [mG] [mA] [mA] [mC] [mU] [mU] [fG] [fC] [fC] [fA] [mA] [mG] [mC] [mU] [mU] [mG] [mG] [mU] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [adema-GalNAc] [adema-GalNAc] [adema-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	391	[MePhosphonate-40-mUs] [fAs] [fCs] [fC] [fA] [mA] [fG] [mC] [mU] [fU] [mG] [mG] [mC] [fA] [mA] [mG] [mU] [mU] [mC] [mUs] [mGs] [mG]	791
LPA-3288-M1	[mAs] [mA] [mC] [mU] [mU] [mG] [mC] [fC] [fA] [fA] [fG] [mC] [mU] [mU] [mG] [mG] [mU] [mC] [mA] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [adema-GalNAc] [adema-GalNAc] [adema-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	392	[MePhosphonate-40-mUs] [fUs] [fGs] [fA] [fC] [mC] [fA] [mA] [mG] [fC] [mU] [mU] [mG] [fG] [mC] [mA] [mA] [mG] [mU] [mUs] [mGs] [mG]	792
LPA-3291-M1	[mUs] [mU] [mG] [mC] [mC] [mA] [mA] [fG] [fC] [fU] [fU] [mG] [mG] [mU] [mC] [mA] [mU] [mC] [mU] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [adema-GalNAc] [adema-GalNAc] [adema-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	393	[MePhosphonate-40-mUs] [fAs] [fGs] [fA] [fU] [mG] [fA] [mC] [mC] [fA] [mA] [mG] [mC] [fU] [mU] [mG] [mG] [mC] [mA] [mAs] [mGs] [mG]	793
LPA-3584-M1	[mAs] [mU] [mG] [mG] [mA] [mC] [mA] [fG] [fA] [fG] [fU] [mU] [mA] [mU] [mC] [mG] [mA] [mG] [mG] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [adema-GalNAc] [adema-GalNAc]	394	[MePhosphonate-40-mUs] [fCs] [fCs] [fU] [fC] [mG] [fA] [mU] [mA] [fA] [mC] [mU] [mC] [fU] [mG] [mU] [mC] [mC] [mA] [mUs] [mGs] [mG]	794

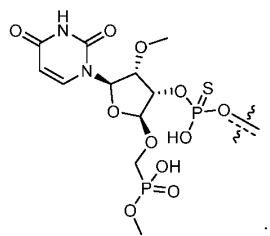
	GalNAc] [ademA- GalNAc] [mG] [mG] [mC] [m U] [mG] [mC]			
LPA-3585-M1	[mUs] [mG] [mG] [mA] [mC] [mA] [mG] [fA] [fG] [fU] [fU] [fU] [mA] [mU] [mC] [mG] [m A] [mG] [mG] [mC] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA- GalNAc] [ademA- GalNAc] [ademA- GalNAc] [mG] [mG] [mC] [m U] [mG] [mC]	395	[MePhosphonate-40- mUs] [fGs] [fCs] [fC] [fU] [m C] [fG] [mA] [mU] [fA] [mA] [m C] [mU] [fC] [mU] [mG] [mU] [m C] [mC] [mAs] [mGs] [mG]	795
LPA-4645-M1	[mUs] [mG] [mG] [mU] [mC] [mA] [mU] [fC] [fU] [fA] [fU] [mG] [mA] [mU] [mA] [mC] [mC] [mA] [mC] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA- GalNAc] [ademA- GalNAc] [ademA- GalNAc] [mG] [mG] [mC] [m U] [mG] [mC]	396	[MePhosphonate-40- mUs] [fGs] [fUs] [fG] [fG] [m U] [fA] [mU] [mC] [fA] [mU] [m A] [mG] [fA] [mU] [mG] [mA] [m C] [mC] [mAs] [mGs] [mG]	796
LPA-4717-M1	[mUs] [mA] [mC] [mU] [mG] [mC] [mA] [fG] [fG] [fA] [fA] [mU] [mC] [mC] [mA] [mG] [mA] [mU] [mU] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA- GalNAc] [ademA- GalNAc] [ademA- GalNAc] [mG] [mG] [mC] [m U] [mG] [mC]	397	[MePhosphonate-40- mUs] [fAs] [fAs] [fU] [fC] [m U] [fG] [mG] [mA] [fU] [mU] [m C] [mC] [fU] [mG] [mC] [mA] [m G] [mU] [mAs] [mGs] [mG]	797
LPA-5510-M1	[mAs] [mG] [mA] [mA] [mA] [mU] [mG] [fU] [fC] [fC] [fU] [mG] [mG] [mA] [mA] [mG] [mC] [mA] [mU] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA- GalNAc] [ademA- GalNAc] [ademA- GalNAc] [mG] [mG] [mC] [m U] [mG] [mC]	398	[MePhosphonate-40- mUs] [fAs] [fUs] [fG] [fC] [m U] [fU] [mC] [mC] [fA] [mG] [m G] [mA] [fC] [mA] [mU] [mU] [m U] [mC] [mUs] [mGs] [mG]	798
LPA-3750-M1	[mGs] [mA] [mC] [mA] [mA] [mC] [mA] [fG] [fA] [fA] [fU] [mA] [mU] [mU] [mA] [mU] [mC] [mC] [mA] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA- GalNAc] [ademA- GalNAc] [ademA- GalNAc] [mG] [mG] [mC] [m U] [mG] [mC]	399	[MePhosphonate-40- mUs] [fUs] [fGs] [fG] [fA] [m U] [fA] [mA] [mU] [fA] [mU] [m U] [mC] [fU] [mG] [mU] [mU] [m G] [mU] [mCs] [mGs] [mG]	799

LPA-2900-M2	[mAs] [mU] [mG] [mG] [mA] [mC] [mA] [fG] [fA] [fG] [fU] [mU] [mA] [mU] [mC] [mA] [mA] [mG] [mG] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA-GalNAc] [ademA-GalNAc] [ademA-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	400	[MePhosphonate-4O-mUs] [fCs] [fC] [fU] [fU] [mG] [fA] [mU] [mA] [fA] [mC] [mU] [mC] [fU] [mG] [mU] [mC] [mC] [mA] [mUs] [mGs] [mG]	800
LPA-3675-M2	[mGs] [mA] [mC] [mA] [mA] [mC] [mA] [fG] [fA] [fA] [fU] [mA] [mU] [mU] [mA] [mU] [mC] [mC] [mA] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA-GalNAc] [ademA-GalNAc] [ademA-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	401	[MePhosphonate-4O-mUs] [fUs] [fG] [fG] [fA] [mU] [fA] [mA] [mU] [fA] [mU] [mU] [mC] [fU] [mG] [mU] [mU] [mG] [mU] [mCs] [mGs] [mG]	801
LPA-2900-M3	[mAs] [mU] [mG] [mG] [mA] [mC] [mA] [fG] [fA] [fG] [fU] [mU] [mA] [mU] [mC] [mA] [mA] [mG] [mG] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA-GalNAc] [ademA-GalNAc] [ademA-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	402	[MePhosphonate-4O-mUs] [fCs] [fC] [mU] [fU] [mG] [fA] [mU] [mA] [fA] [mC] [mU] [mC] [fU] [mG] [mU] [mC] [mC] [mA] [mUs] [mGs] [mG]	802
LPA-3675-M3	[mGs] [mA] [mC] [mA] [mA] [mC] [mA] [fG] [fA] [fA] [fU] [mA] [mU] [mU] [mA] [mU] [mC] [mC] [mA] [mA] [mG] [mC] [mA] [mG] [mC] [mC] [mG] [ademA-GalNAc] [ademA-GalNAc] [ademA-GalNAc] [mG] [mG] [mC] [mU] [mG] [mC]	403	[MePhosphonate-4O-mUs] [fUs] [fG] [mG] [fA] [mU] [fA] [mA] [mU] [fA] [mU] [mU] [mC] [fU] [mG] [mU] [mU] [mG] [mU] [mCs] [mGs] [mG]	803

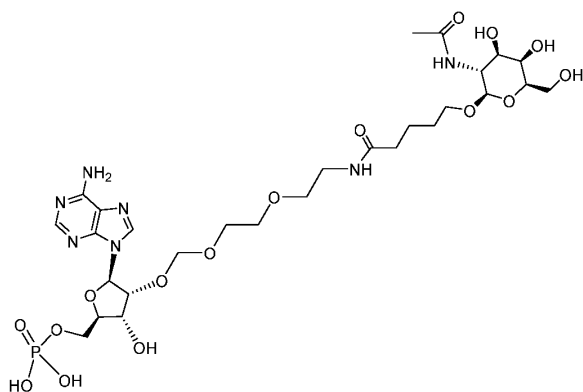
Modifications in Table 6:

mC, mA, mG, mU=2'-OMe ribonucleosides; fA, fC, fG, fU=2'-F ribonucleosides; s=phosphorothioate;

MePhosphonate-4O-mUs =



ademA-GalNAc = GalNAc attached to an adenine nucleotide:



CLAIMS

What is claimed is:

1. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.
2. The RNAi oligonucleotide of claim 1, wherein the sense strand is 15 to 50 nucleotides in length.
3. The RNAi oligonucleotide of claims 1 or 2, wherein the sense strand is 18 to 36 nucleotides in length.
4. The RNAi oligonucleotide of any one of claims 1 to 3, wherein the antisense strand is 15 to 30 nucleotides in length.
5. The RNAi oligonucleotide of any one of claims 1 to 4, wherein the antisense strand is 22 nucleotides in length and wherein antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length.
6. The RNAi oligonucleotide of any one of claims 1 to 5, wherein the region of complementarity is at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.
7. The RNAi oligonucleotide of any one of claims 1 to 6, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length.
8. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID

NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

9. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

10. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

11. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

12. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

13. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3'

end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

14. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

15. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

16. The RNAi oligonucleotide of any one of claims 7 and 13-15, wherein L is a triloop or a tetraloop.

17. The RNAi oligonucleotide of claim 16, wherein L is a tetraloop.

18. The RNAi oligonucleotide of claim 17, wherein the tetraloop comprises the sequence 5'-GAAA-3'.

19. The RNAi oligonucleotide of any one of claims 16-18, wherein the S1 and S2 are 1-10 nucleotides in length and have the same length.
20. The RNAi oligonucleotide of claim 19, wherein S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length.
21. The RNAi oligonucleotide of claim 20, wherein S1 and S2 are 6 nucleotides in length.
22. The RNAi oligonucleotide of any one of claims 16 to 21, wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 190).
23. The RNAi oligonucleotide of any one of claims 1 to 22, wherein the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length.
24. The RNAi oligonucleotide of claim 23, wherein the 3' overhang sequence is 2 nucleotides in length, optionally wherein the 3' overhang sequence is GG.
25. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.
26. The RNAi oligonucleotide of claim 25, wherein the modified nucleotide comprises a 2'-modification.
27. The RNAi oligonucleotide of claim 26, wherein the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid.
28. The RNAi oligonucleotide of any one of claims 25 to 27, wherein all nucleotides comprising the oligonucleotide are modified, optionally wherein the modification is a 2'-modification selected from 2'-fluoro and 2'-O-methyl.

29. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.
30. The RNAi oligonucleotide of claim 29, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.
31. The RNAi oligonucleotide of any one of the preceding claims, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.
32. The RNAi oligonucleotide of claim 31, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonyl phosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.
33. The RNAi oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.
34. The RNAi oligonucleotide of claim 33, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid.
35. The RNAi oligonucleotide of claim 33, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.
36. The RNAi oligonucleotide of claim 35, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.
37. The RNAi oligonucleotide of any one of claims 16 to 32, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.
38. The RNAi oligonucleotide of any one of claims 1 to 37, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, and 403.

39. The RNAi oligonucleotide of any one of claims 1 to 38, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, and 803.

40. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 393 and 793, respectively;
- (b) SEQ ID NOs: 388 and 788, respectively;
- (c) SEQ ID NOs: 389 and 789, respectively;
- (d) SEQ ID NOs: 390 and 790, respectively;
- (e) SEQ ID NOs: 391 and 791, respectively;
- (f) SEQ ID NOs: 392 and 792, respectively;
- (g) SEQ ID NOs: 394 and 794, respectively;
- (h) SEQ ID NOs: 395 and 795, respectively;
- (i) SEQ ID NOs: 396 and 796, respectively;
- (j) SEQ ID NOs: 397 and 797, respectively;
- (k) SEQ ID NOs: 398 and 798, respectively;
- (l) SEQ ID NOs: 399 and 799, respectively;
- (m) SEQ ID NOs: 400 and 800, respectively;
- (n) SEQ ID NOs: 401 and 801, respectively;
- (o) SEQ ID NOs: 402 and 802, respectively; and
- (p) SEQ ID NOs: 403 and 803, respectively.

41. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 393, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 793.

42. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 388, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 788.

43. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 389, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 789.

44. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 390, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 790.

45. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 391, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 791.

46. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 392, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 792.

47. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 394, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 794.

48. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 395, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 795.

49. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 396, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 796.

50. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 397, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 797.

51. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 398, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 798.

52. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 399, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 799.

53. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 400, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 800.

54. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 401, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 801.

55. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 402, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 802.

56. The RNAi oligonucleotide of any one of claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 403, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 803.

57. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

58. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

59. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

60. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise one or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

61. A method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of the RNAi oligonucleotide of any one of the preceding claims, or pharmaceutical composition thereof, thereby treating the subject.

62. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of claims 1 to 60, and a pharmaceutically acceptable carrier, delivery agent or excipient.

63. A method of delivering an oligonucleotide to a subject, the method comprising administering pharmaceutical composition of claim 61 to the subject.

64. A method for reducing *LPA* expression in a cell, a population of cells or a subject, the method comprising the step of:

i. contacting the cell or the population of cells with the RNAi oligonucleotide of any one of claims 1 to 60, or the pharmaceutical composition of claim 62; or

ii. administering to the subject the RNAi oligonucleotide of any one of claims 1 to 83, or the pharmaceutical composition of claim 85.

65. The method of claim 64, wherein reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of *LPA* protein, or both.

66. The method of claim 64 or 65, wherein the subject has a disease, disorder or condition associated with *LPA* expression.

67. The method of claim 66, wherein the disease, disorder or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

68. The method of any one of claims 61 and 63 to 67, wherein the RNAi oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

69. A method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *LPA* mRNA target sequence of any one of SEQ ID NOs: 4-387, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

70. A method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in **Table 5**, or pharmaceutical composition thereof, thereby treating the subject.

71. A method for treating a subject having a disease, disorder or condition associated with *LPA* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein

the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 393 and 793, respectively;
- (b) SEQ ID NOs: 388 and 788, respectively;
- (c) SEQ ID NOs: 389 and 789, respectively;
- (d) SEQ ID NOs: 390 and 790, respectively;
- (e) SEQ ID NOs: 391 and 791, respectively;
- (f) SEQ ID NOs: 392 and 792, respectively;
- (g) SEQ ID NOs: 394 and 794, respectively;
- (h) SEQ ID NOs: 395 and 795, respectively;
- (i) SEQ ID NOs: 396 and 796, respectively;
- (j) SEQ ID NOs: 397 and 797, respectively;
- (k) SEQ ID NOs: 398 and 798, respectively;
- (l) SEQ ID NOs: 399 and 799, respectively;
- (m) SEQ ID NOs: 400 and 800, respectively;
- (n) SEQ ID NOs: 401 and 801, respectively;
- (o) SEQ ID NOs: 402 and 802, respectively; and
- (p) SEQ ID NOs: 403 and 803, respectively.

72. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 393, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 793.

73. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 388, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 788.

74. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 389, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 789.

75. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 390, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 790.

76. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 391, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 791.

77. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 392, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 792.

78. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 394, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 794.

79. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 395, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 795.

80. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 396, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 796.

81. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 397, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 797.

82. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 398, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 798.

83. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 399, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 799.

84. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 400, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 800.

85. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 401, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 801.

86. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 402, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 802.

87. The method of claim 71, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 403, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 803.

88. The method of any one of claims 69 to 87, wherein the disease, disorder or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

89. Use of the RNAi oligonucleotide of any one of claims 1 to 60, or the pharmaceutical composition of claim 62, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with *LPA* expression, optionally for the treatment of a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

90. The RNAi oligonucleotide of any one of claims 1 to 60, or the pharmaceutical composition of claim 62, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *LPA* expression, optionally for the treatment of a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

91. A kit comprising the RNAi oligonucleotide of any one of claims 1 to 60, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with *LPA* expression.

92. The use of claim 89, the RNAi oligonucleotide or pharmaceutical composition for use, or adaptable for use, of claim 90, or the kit of claim 91, wherein the disease, disorder or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.