# 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

**[0005]** Examples 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 one aspect, 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 examples, the sense strand is 15 to 50 nucleotides in length. In some examples, the sense strand is 18 to 36 nucleotides in length.

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

**[0009]** In any of the foregoing or related examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 another aspect, the present disclosure provides an RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length, optionally 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. In further examples, 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 examples, 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 examples, 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 examples, 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 examples, L is a triloop or a tetraloop. In some examples, L is a tetraloop. In some examples, the tetraloop comprises the sequence 5'-GAAA-3'.

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

**[0022]** In any of the foregoing or related examples, the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length. In some examples, 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 examples, the oligonucleotide comprises at least one modified nucleotide. In some examples, the modified nucleotide comprises a 2′-modification. In some examples, 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 examples, 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 examples, the oligonucleotide comprises at least one modified internucleotide linkage. In some examples, the at least one modified internucleotide linkage is a phosphorothioate linkage.

**[0025]** In any of the foregoing or related examples, the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog. In some examples, 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 examples, at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands. In some examples, each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid. In some examples, each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety. In some examples, the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety. In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 another aspect, 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 all nucleotides comprising the sense strand and antisense strand are modified, optionally 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. In some examples, 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 examples, 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 examples, 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 another aspect, 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 examples, 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 as described herein, or pharmaceutical composition thereof, thereby treating the subject.

**[0036]** In a further aspect, the present disclosure provides an RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in **Table 5**, or pharmaceutical composition thereof. In another aspect, the disclosure provides a pharmaceutical composition comprising a RNAi oligonucleotide described herein, and a pharmaceutically acceptable carrier, delivery agent or excipient.

**[0037]** In other examples, 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 examples, 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 examples, reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of LPA protein, or both. In some examples, the subject has a disease, disorder or condition associated with *LPA* expression. In some examples, the disease, disorder, or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH. In some examples, the RNAi

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

**[0039]** In a further aspect, the present disclosure provides a use of the RNAi oligonucleotide as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having a disease, disorder or condition associated with *LPA* expression, thereby treating the subject. In a further aspect, the present disclosure provides a method for reducing *LPA* expression in a cell or a population of cells, the method comprising the step of: i. contacting the cell or the population of cells with the RNAi oligonucleotide as described herein, or the pharmaceutical composition as described herein; optionally wherein reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of LPA protein, or both. In a further aspect, the present disclosure provides a use of the RNAi oligonucleotide as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for reducing *LPA* expression; optionally wherein reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of LPA protein, or both. In a further aspect, the present disclosure provides the RNAi oligonucleotide as described herein, or the pharmaceutical composition as described herein for use in therapy. In another example, 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 example, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the disease, disorder, or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD and NASH.

**[0044]** In some examples, 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 examples, 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 another aspect, 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 examples, 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.

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, optionally, wherein the sense strand is 18 to 36 nucleotides in length; and/or wherein the antisense strand is 15 to 30 nucleotides in length, optionally, 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; and/or wherein the region of complementarity is at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.

3. The RNAi oligonucleotide of claim 1 or 2, 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.

4. An RNAi oligonucleotide for reducing *LPA* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length, optionally 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.

5. 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.

6. The RNAi oligonucleotide of any one of claims 3-5, wherein L is a triloop or a tetraloop; optionally, wherein the tetraloop comprises the sequence 5’-GAAA-3’.

7. The RNAi oligonucleotide of claim 6, wherein the S1 and S2 are 1-10 nucleotides in length and have the same length; optionally, wherein S1 and S2 are 6 nucleotides in length.

8. The RNAi oligonucleotide of claim 6 or 7, wherein the stem-loop comprises the sequence 5’-GCAGCCGAAAGGCUGC-3’ (SEQ ID NO: 190).

9. The RNAi oligonucleotide of any one of claims 1 to 8, wherein the antisense strand comprises a 3’ overhang sequence of one or more nucleotides in length; optionally, wherein the 3’ overhang sequence is 2 nucleotides in length, optionally wherein the 3’ overhang sequence is GG.

10. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide; optionally wherein the modified nucleotide comprises a 2′-modification, and/or, 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.

11. The RNAi oligonucleotide of claim 10, wherein all nucleotides comprising the oligonucleotide are modified, optionally wherein the modification is a 2’-modification selected from 2’-fluoro and 2’-O-methyl.

12. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage; optionally, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

13. 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; optionally, 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.

14. 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; optionally wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety; optionally, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.

15. The RNAi oligonucleotide of any one of claims 6 to 14, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

16. The RNAi oligonucleotide of any one of claims 1 to 15, 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, and/or 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.

17. The RNAi oligonucleotide of any one of claims 1 to 16, 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.

18. 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, optionally 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.

19. 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.

20. An RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in **Table 5**, or pharmaceutical composition thereof.

21. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of claims 1 to 20, and a pharmaceutically acceptable carrier, delivery agent or excipient.

22. Use of the RNAi oligonucleotide of any one of claims 1-20, or the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a subject having a disease, disorder or condition associated with *LPA* expression, thereby treating the subject.

23. A method for reducing *LPA* expression in a cell or a population of cells, 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 20, or the pharmaceutical composition of claim 21; optionally wherein reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of LPA protein, or both.

24. Use of the RNAi oligonucleotide of any one of claims 1 to 20, or the pharmaceutical composition of claim 21 in the manufacture of a medicament for reducing *LPA* expression; optionally wherein reducing *LPA* expression comprises reducing an amount or level of *LPA* mRNA, an amount or level of LPA protein, or both.

25. The use of claim 22 or 24, wherein the subject has a disease, disorder or condition associated with *LPA* expression; optionally, wherein the disease, disorder or condition associated with *LPA* expression is a cardiometabolic disease, optionally atherosclerosis, dyslipidemia, NAFLD or NASH.

26. The use of any one of claims 22 and 24-25, wherein the RNAi oligonucleotide, or pharmaceutical composition, is to be administered in combination with a second composition or therapeutic agent.

27. The RNAi oligonucleotide of any one of claims 1-20, or the pharmaceutical composition of claim 21 for use in therapy.

28. A kit comprising the RNAi oligonucleotide of any one of claims 1 to 20, 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.