

**POLYNUCLEIC ACID MOLECULES FOR INHIBITING EXPRESSION OF LP(A),
PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF**

CROSS-REFERENCES

[0001] This application claims the benefit of U.S. Provisional Application No. 63/371,167 filed on August 11, 2022, and U.S. Provisional Application No. 63/449,914 filed on March 3, 2023, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] The discovery of RNA interference (RNAi) as a cellular mechanism that selectively degrades mRNAs allows for both the targeted manipulation of cellular phenotypes in cell culture and the potential for development of directed therapeutics (Behlke, 2006, Mol. Ther. 13, 644-670; Xie et al., 2006, Drug Discov. Today 11, 67-73).

[0003] Lipoprotein(a) (Lp(a)) is a lipoprotein composed of an LDL (low-density lipoprotein) lipid core, apolipoprotein B (apo B), and a unique apolipoprotein, apo(a). Lp(a) is considered one of the most common independent genetically inherited causal risk factors for cardiovascular disease (CVD). Accordingly, there is a need for developing an effective Lp(a) inhibitor. The polynucleic acid molecules, conjugates thereof, and methods described herein satisfy this need and provide related advantages.

INCORPORATION BY REFERENCE

[0004] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

SUMMARY OF THE DISCLOSURE

[0005] Disclosed herein, in certain aspects, is a polynucleic acid molecule for modulating expression of lipoprotein(a) (Lp(a)) gene, comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 1-154. In some cases, the sense strand comprises

comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 309-462. In some cases, the antisense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, 20, 21, or 22 consecutive sequences of a nucleic acid sequence selected from SEQ ID NOs: 1-154, with no more than 1, 2, 3, or 4 mismatches. In some cases, the sense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, or 20 consecutive sequences from a nucleic acid sequence selected from SEQ ID NOs: 309-462, with no more than 1, 2, 3, or 4 mismatches. In some cases, the sense strand comprises one of SEQ ID NOs: 309-462 and the antisense strand comprises a nucleic acid sequence that is selected from SEQ ID NOs: 1-154

[0006] In some cases, the sense strand comprises at least two consecutive modified internucleotide linkages at the 5' end. In some cases, the antisense strand comprises at least two consecutive modified internucleotide linkages at the 5' end and/or 3' end. In some cases, the modified internucleotide linkage is a phosphorothioate linkage. In some cases, the modified internucleotide linkage comprises a stereochemically enriched phosphorothioate internucleotide linkage. In some cases, the modified internucleotide linkage is an S_P chiral internucleotide phosphorothioate linkage. In some cases, the polynucleic acid comprises a plurality of modified internucleotide linkages, and at least 1, 2, 3, or 4 of the plurality of modified internucleotide linkages are stereochemically enriched phosphorothioate internucleotide linkages. In some cases, at least one stereochemically enriched phosphorothioate is disposed between two consecutive nucleosides that are two of six 5' or 3'-terminal nucleosides of the sense strand or the antisense strand. In some cases, the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', wherein n stands for a 2'-O-methyl modified nucleotide, and wherein Nf stands for a 2'-fluoro modified nucleotide.

[0007] In some cases, the sense strand or antisense strand is about 19-25, or about 21-23 nucleotides in length.

[0008] In some cases, the sense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 463-616. In some cases, the antisense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 155-308. In some cases, the sense strand comprises a sequence selected from a nucleic acid sequence of SEQ ID NOs: 463-616, and the antisense strand comprises a sequence selected from a nucleic acid sequence of SEQ ID NOs: 155-308.

[0009] In another aspect, provided herein is polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises :

(a) an antisense strand comprising the nucleotide sequence of UAGAUGACCAAGCUUGGCAGGUC (SEQ ID NO: 4) and a sense strand comprising the nucleotide sequence of CCUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 312); (b) an antisense strand comprising the nucleotide sequence of UAUAGAUGACCAAGCUUGGCAGG (SEQ ID NO: 5) and a sense strand comprising the nucleotide sequence of UGCCAAGCUUGGUCAUCUAUA (SEQ ID NO: 313); (c) an antisense strand comprising the nucleotide sequence of UCAUAGAUGACCAAGCUUGGCAG (SEQ ID NO: 6) and a sense strand comprising the nucleotide sequence of GCCAAGCUUGGUCAUCUAUGA (SEQ ID NO: 314); (d) an antisense strand comprising the nucleotide sequence of UCGACGGCAGUCCCUUCUGCGUC (SEQ ID NO: 11) and a sense strand comprising the nucleotide sequence of CGCAGAAGGGACUGCCGUCGA (SEQ ID NO: 319); (e) an antisense strand comprising the nucleotide sequence of UUCUAGGCUUGGAACCGGGGUA (SEQ ID NO: 18) and a sense strand comprising the nucleotide sequence of ACCCGGUUCCAAGCCUAGAA (SEQ ID NO: 326); (f) an antisense strand comprising the nucleotide sequence of UAGCCUCUAGGCUUGGAACCGGG (SEQ ID NO: 21) and a sense strand comprising the nucleotide sequence of CGGUUCCAAGCCUAGAGGCUA (SEQ ID NO: 329); (g) an antisense strand comprising the nucleotide sequence of UUUACCGUGGUAGCACUCCUGCA (SEQ ID NO: 44) and a sense strand comprising the nucleotide sequence of CAGGAGUGCUACCACGGUAAA (SEQ ID NO: 352); (h) an antisense strand comprising the nucleotide sequence of UUGUCCAUAUACCGUGGUAGCACU (SEQ ID NO: 47) and a sense strand comprising the nucleotide sequence of UGCUACCACGGUAAUGGACAA (SEQ ID NO: 355); (i) an antisense strand comprising the nucleotide sequence of UCUCUGUCCAUAUACCGUGGUAGC (SEQ ID NO: 49) and a sense strand comprising the nucleotide sequence of UACCACGGUAAUGGACAGAGA (SEQ ID NO: 357); (j) an antisense strand comprising the nucleotide sequence of UAUUGUGUCAGGUUGCAGUACUC (SEQ ID NO: 60) and a sense strand comprising the nucleotide sequence of GUACUGCAACCUGACACAAUA (SEQ ID NO: 368); (k) an antisense strand comprising the nucleotide sequence of UUGCGUCUGAGCAUUGUGUCAGG (SEQ ID NO: 64) and a sense strand comprising the nucleotide sequence of UGACACAAUGCUCAGACGCAA (SEQ ID NO: 372); (l) an antisense strand comprising the nucleotide sequence of UUAACUCUGUCCAUAUUGGUAGU (SEQ ID NO: 88) and a sense strand comprising the nucleotide sequence of UACCAUUAUGGACAGAGUUA (SEQ ID NO: 89);

396); (m) an antisense strand comprising the nucleotide sequence of UCCAAGCUUGGCAAGUUCUCCU (SEQ ID NO: 89) and a sense strand comprising the nucleotide sequence of GAAGAACUUGCCAAGCUUGGA (SEQ ID NO: 397); (n) an antisense strand comprising the nucleotide sequence of UAGAUGACCAAGCUUGGCAAGUU (SEQ ID NO: 90) and a sense strand comprising the nucleotide sequence of CUUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 398); or (o) an antisense strand comprising the nucleotide sequence of UGGUCCGACUAUGCUGGUGUGGU (SEQ ID NO: 98) and a sense strand comprising the nucleotide sequence of CACACCAGCAUAGUCGGACCA (SEQ ID NO: 406).

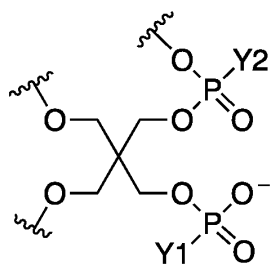
[0010] In another aspect, provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises: (a) an antisense strand comprising the nucleotide sequence of usAfsaugAfccaaGfcUfuGfgcaggsusc (SEQ ID NO: 158) and a sense strand comprising the nucleotide sequence of cscsugccAfaGfcUfuggucauca (SEQ ID NO: 466); (b) an antisense strand comprising the nucleotide sequence of usAfsuagaUfgaccAfaGfcUfuggcasgsg (SEQ ID NO: 159) and a sense strand comprising the nucleotide sequence of usgsccaaGfcUfuGfgucaucaua (SEQ ID NO: 467); (c) an antisense strand comprising the nucleotide sequence of usCfsauagAfugacCfaAfgCfuuggcsasg (SEQ ID NO: 160) and a sense strand comprising the nucleotide sequence of gscscaagCfuUfgGfucaucauga (SEQ ID NO: 468); (d) an antisense strand comprising the nucleotide sequence of usCfsgacgGfcaguCfcCfuUfcugcgsusc (SEQ ID NO: 165) and a sense strand comprising the nucleotide sequence of csgscagaAfgGfgAfcugccgucga (SEQ ID NO: 473); (e) an antisense strand comprising the nucleotide sequence of usUfscuagGfcuugGfaAfcCfggggusasa (SEQ ID NO: 172) and a sense strand comprising the nucleotide sequence of ascscgGfuUfcCfaagccuagaa (SEQ ID NO: 480); (f) an antisense strand comprising the nucleotide sequence of usAfsgccuCfuaggCfuUfgGfaaccgsgsg (SEQ ID NO: 175) and a sense strand comprising the nucleotide sequence of csgsguucCfaAfgCfcuagaggcua (SEQ ID NO: 483); (g) an antisense strand comprising the nucleotide sequence of usUfsuaccGfugguAfgCfaCfuccugscsa (SEQ ID NO: 198) and a sense strand comprising the nucleotide sequence of csasggagUfgCfuAfccacgguaaa (SEQ ID NO: 506); (h) an antisense strand comprising the nucleotide sequence of usUfsguccAfuacCfgUfgGfuagcascu (SEQ ID NO: 201) and a sense strand comprising the nucleotide sequence of usgsuacCfaCfgGfuuauggacaa (SEQ ID NO: 509); (i) an antisense strand comprising the nucleotide sequence of usCfsucugUfccauUfaCfcGfugguasgsc (SEQ ID NO: 203) and a sense strand comprising the nucleotide sequence of usasccacGfgUfaAfggacagaga (SEQ ID NO: 511); (j) an antisense strand comprising the nucleotide sequence of

usAfsuuguGfucagGfuUfgCfaguacsusc (SEQ ID NO: 214) and a sense strand comprising the nucleotide sequence of gsusacugCfaAfcCfugacacaa (SEQ ID NO: 522); (k) an antisense strand comprising the nucleotide sequence of usUfsgcguCfugagCfaUfuGfugucasgsg (SEQ ID NO: 218) and a sense strand comprising the nucleotide sequence of usgsacacAfaUfgCfucagacgcaa (SEQ ID NO: 526); (l) an antisense strand comprising the nucleotide sequence of usUfssaacuCfugucCfaUfaAfugguasgsu (SEQ ID NO: 242) and a sense strand comprising the nucleotide sequence of usasccauUfaUfgGfacagaguuaa (SEQ ID NO: 550); (m) an antisense strand comprising the nucleotide sequence of usCfscaagCfuuggCfaAfgUfucuucscsu (SEQ ID NO: 243) and a sense strand comprising the nucleotide sequence of gsasagaaCfuUfgCfcaagcuugga (SEQ ID NO: 551); (n) an antisense strand comprising the nucleotide sequence of usAfsgaugAfccaaGfcUfuGfgcaagsusu (SEQ ID NO: 244) and a sense strand comprising the nucleotide sequence of csusugccAfaGfcUfuggucaucua (SEQ ID NO: 552); or (o) an antisense strand comprising the nucleotide sequence of usGfsguccGfacuaUfgCfuGfgugugsgsu (SEQ ID NO: 252) and a sense strand comprising the nucleotide sequence of csascaccAfgCfaUfagucggacca (SEQ ID NO: 560),

wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

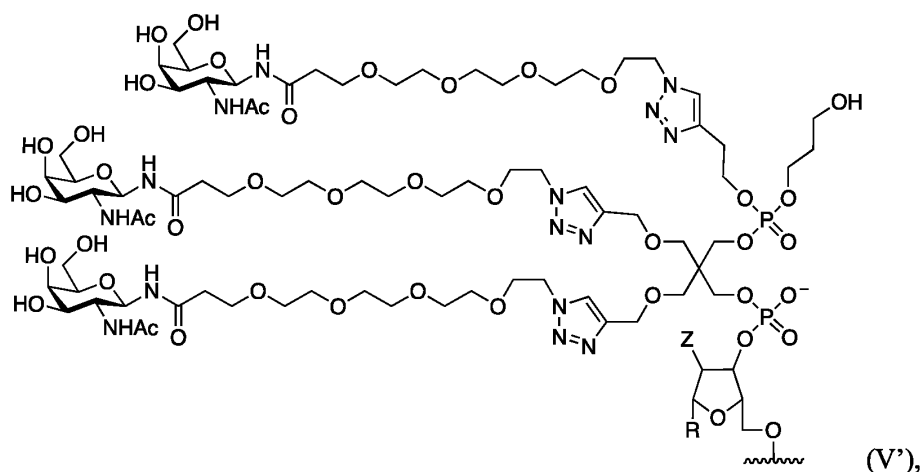
[0011] In another aspect, provided herein is a polynucleic acid molecule conjugate for modulating expression of lipoprotein(a) gene (Lp(a)), wherein the polynucleic acid molecule conjugate comprises a polynucleic acid molecule described herein and an asialoglycoprotein receptor targeting moiety. In some cases, the asialoglycoprotein receptor targeting moiety comprises N-Acetylgalactosamine (GalNAc) or galactose. In some cases, the GalNAc comprises an anomeric carbon bonded to trivalent, tetravalent linker, pentavalent, or hexavalent linker, wherein the anomeric carbon is part of a hemiaminal group.

[0012] In some cases, the polynucleic acid molecule and the asialoglycoprotein receptor targeting moiety is coupled via a linker. In some cases, the linker is a cleavable linker. In some cases, the

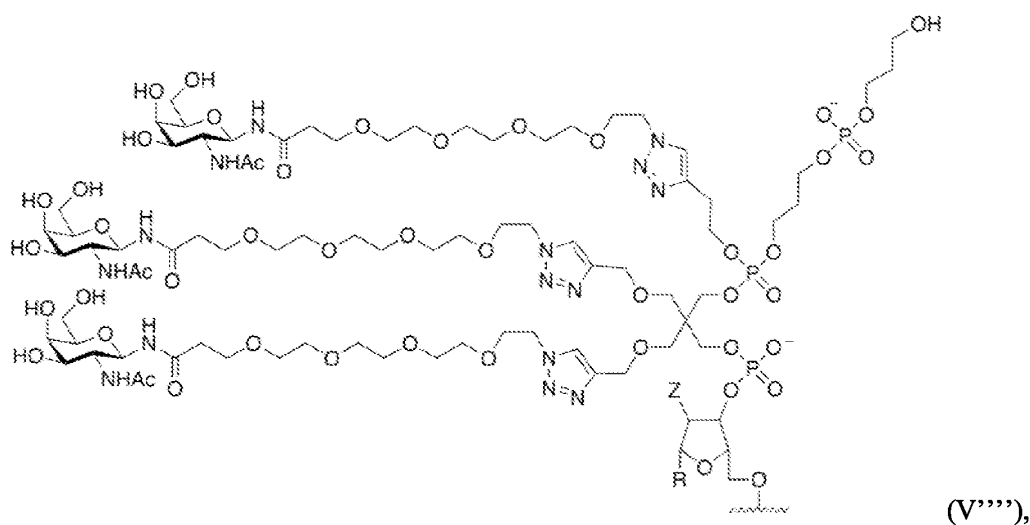


linker comprises formula (IV) below, wherein at least one of Y1 and Y2 is a nucleotide in the polynucleic acid molecule. In some cases, the Y1 is the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule.

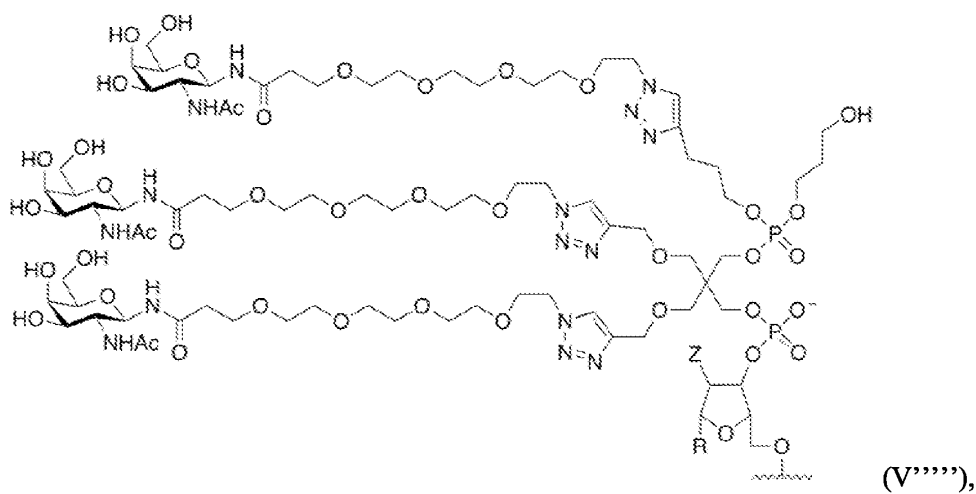
[0013] In some cases, the linker and the asialoglycoprotein receptor targeting moiety with the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule are shown in Formula (V'), Formula (V'''), Formula (V'''''), or Formula (V'''''):



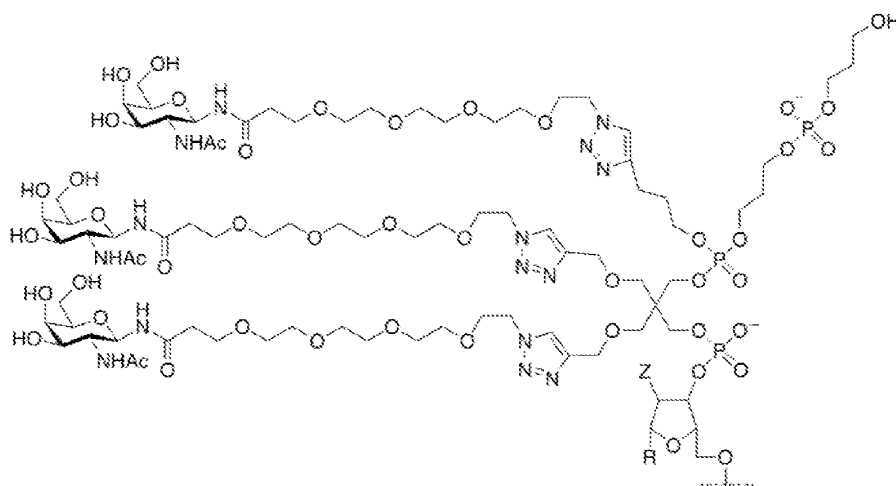
wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others;



wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



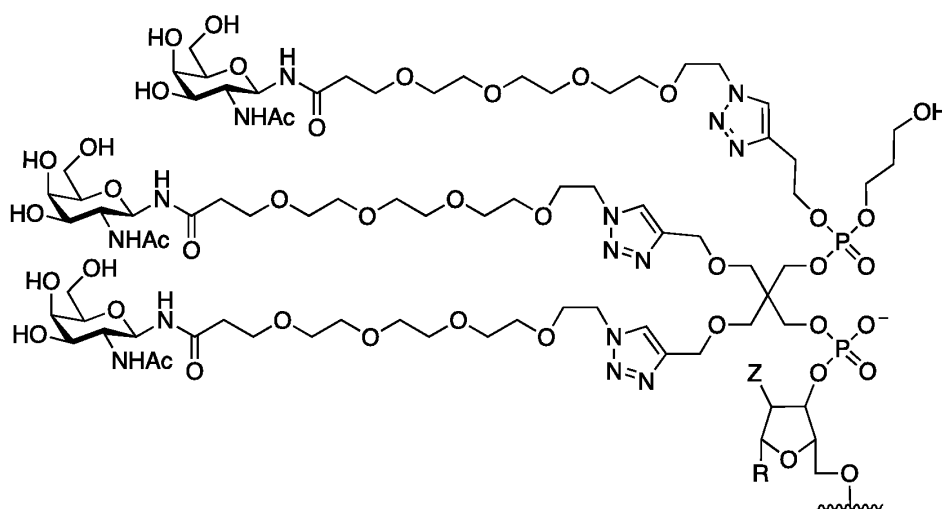
wherein Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others; or



(V'''''), wherein

Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0014] In some cases, the linker and the asialoglycoprotein receptor targeting moiety with the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule are shown in Formula (V'):



(V'), wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0015] In another aspect, provided herein is a pharmaceutical composition comprising a polynucleic acid molecule described herein or a polynucleic acid molecule conjugate described herein, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical composition

is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.

[0016] In another aspect, provided herein is method of modulating expression of lipoprotein(a) (Lp(a)) gene in a subject in need thereof, comprising: administering to the subject a polynucleic acid molecule described herein, a polynucleic acid molecule conjugate described herein, or a pharmaceutical composition described herein, thereby modulating the expression of Lp(a) gene in the subject in need thereof.

[0017] In another aspect, provided herein is a method for treating or preventing a cardiovascular disease or a lipid disorder, comprising: administering to the subject a polynucleic acid molecule described herein, a polynucleic acid molecule conjugate described herein, or a pharmaceutical composition described herein, thereby modulating the expression of Lp(a) gene in the subject in need thereof. In some cases, the cardiovascular disease is coronary artery disease, acute myocardial infarction, asymptomatic carotid atherosclerosis, stroke, atrial fibrillation, hypercholesterolemia, or peripheral artery occlusive disease. In some cases, the lipid disorder is hyperlipidemia or hypercholesterolemia.

[0018] In some cases, the polynucleic acid molecule is administered at a dose sufficient to decrease the expression of Lp(a) gene in a cell of said subject or to decrease plasma Lp(a) level of said subject by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% compared to a control.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative aspects, in which the principles of the disclosure are utilized, and the accompanying drawings below.

[0020] **FIGs. 1A-1VV** show dose responses of siRNA compositions on Lp(a) expression levels in primary human hepatocytes (PHH).

[0021] **FIG. 2** shows % change in serum Lp(a) level from base line (Day -1) in cynomolgus monkeys.

[0022] **FIG. 3** shows % change in serum Lp(a) level from base line (Day -1) in cynomolgus monkeys.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0023] Lp(a) gene (LPA) is located on chromosome 6q26-q27 is the major gene locus for Lp(a) concentrations in all populations (F. Kronenberg et al., J Intern Med, 273 (1) (2013)). LPA gene is one of the strongest monogenic risk factors for CVD (S. Tsimikas, J Am Coll Cardiol, 69 (6) (2017)). The LPA gene is highly expressed in liver with dramatic decrease as well as increase in Lp(a) observed after liver transplant (A.A. Damluji et al., Journal of clinical lipidology, 10 (2) (2016)).

[0024] Lipoprotein (a) (Lp(a)) is a low-density lipoprotein-like particle formed by the association of apolipoprotein (a) (apo(a)) with apolipoprotein B (apo B). The apo(a) protein is covalently linked to apo B in the assembled Lp(a) particle via a disulfide bond. Lp(a) carries atherosclerosis-causing cholesterol and binds atherogenic pro-inflammatory oxidized phospholipids as a preferential carrier of oxidized phospholipids in human plasma, which facilitate inflammation reactions.

[0025] The plasma level of Lp(a) is primarily determined by the LPA gene encoding apo(a) (S. Tsimikas, J Am Coll Cardiol, 69 (6) (2017)). The Lp(a) level varies between individuals and is directly proportional to CVD risk. Elevated plasma levels of Lp(a) are associated with increased risk for atherosclerosis and its manifestations, which may include hypercholesterolemia (Seed et al., N. Engl. J. Med., 1990, 322, 1494-1499), myocardial infarction (Sandkamp et al., Clin. Chem., 1990, 36, 20-23), and thrombosis (Nowak-Gottl et al., Pediatrics, 1997, 99, E11). Therefore, inhibition of LPA is viewed as a potential therapeutic strategy to treat CVD.

[0026] Described herein is a polynucleic acid molecule for modulating expression of Lp(a) gene, comprising a nucleic acid sequence selected from Table 1 or Table 2. In some instances, the polynucleic acid molecule is a single-stranded nucleic acid molecule. In some instances, the polynucleic acid molecule is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand. Accordingly, provided herein are various target regions of human Lp(a) mRNA the polynucleic acid molecule described herein hybridizes to. The polynucleic acid molecule described herein can be a modified polynucleic acid molecule. For example, the modified polynucleic acid molecule can comprise a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, or a modified internucleotide linkage such as a phosphorothioate linkage. In some aspects, provided herein is the polynucleic acid conjugated with a targeting moiety described herein.

[0027] Also described herein is a method of modulating expression of Lp(a) mRNA or protein in a subject. Described further herein is a method of modulating LDL and/or cholesterol in a subject in need thereof.

Definition

[0028] The singular form “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes one or more cells, including mixtures thereof. “A and/or B” is used herein to include all of the following alternatives: “A”, “B”, “A or B”, and “A and B.”

[0029] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0030] Certain ranges are presented herein with numerical values being preceded by the term “about.” The term “about” is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number.

[0031] “Percent (%) sequence identity” or “Percent (%) identity” with respect to the nucleic acid sequences identified herein is defined as the percentage of nucleic acid in a candidate sequence that are identical with the nucleic acid sequence being compared, after aligning the sequences considering any conservative substitutions as part of the sequence identity.

[0032] All ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, and so forth. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, and the like. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 articles refers to groups having 1, 2, or 3 articles. Similarly, a group having 1-5 articles refers to groups having 1, 2, 3, 4, or 5 articles, and so forth.

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the polynucleic acid molecules, the polynucleic acid molecule conjugates, the pharmaceutical compositions, the methods and other aspects belong.

[0034] As used herein, the term “complementary” indicates a sufficient degree of complementarity between two nucleic acid molecules that bind stably and specifically to avoid nonspecific binding.

[0035] As used herein, the term “polynucleic acid” and the term “polynucleotide” are interchangeably used to refer a chain of nucleotides. The term “nucleotide” includes a sequence “G,” “C,” “A,” “T” and “U” each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine and uracil as a base. In some instances, the “nucleotide” can refer to a modified nucleotide (e.g., with modified sugar moiety, modified base, modified internucleotide linkage, or combination thereof, including, but not limited to 2’-modified nucleotide, LNA, ENA, BNA, UNA, GNA etc.) In some instances, the “nucleotide” can refer to a modified nucleotide with a non-canonical base (e.g. including, but not limited to, 2-thiouridine, 2-thiothymidine, inosine, 2-aminopurine, 2,6-diaminopurine, dihydrouridine, 4-thiouridine, 4-thiothymidine, 2-thiocytidine).

[0036] As used herein, a “subject” can be any mammal, including a human and a non-human primate.

[0037] A “subject in need thereof”, refers to a subject having a Lp(a) related disorder or symptoms thereof, including but not limited to, CVD or a lipid disorder, or a subject having an increased risk of developing Lp(a) related disorder or symptoms thereof, including but not limited to, a CVD or lipid disorder relative to the population at large. In some instances, a subject in need thereof has coronary heart disease or atherosclerosis, or symptoms thereof. In some instances, a subject in need thereof has hyperlipidemia or hypercholesterolemia, or symptoms thereof. In some instances, a subject in need thereof is being administered or has been administered a drug different from the polynucleic acid molecules or conjugates disclosed herein, for treating or preventing a CVD or lipid disorder. For example, a subject in need thereof is being administered or has been administered atorvastatin.

[0038] The term “condition,” as used herein, includes diseases, disorders, and susceptibilities. In some cases, the condition is an Lp(a) related disorder, atherosclerotic vascular disease, or symptoms thereof. In some cases, the condition is a hypertriglyceridemia or symptoms thereof.

[0039] The term “atherosclerosis” or “atherosclerotic vascular disease,” as used herein, refers to a disease in which the inside of an artery narrows due to the buildup of plaque. In some instances, it may result in coronary artery disease, stroke, peripheral artery disease, or kidney problems.

[0040] The term “cardiovascular disease” or “CVD” refers to all types of diseases that affect the heart or blood vessels, including coronary heart disease (clogged arteries), which can cause heart attacks, stroke, congenital heart defects and peripheral artery disease. A CVD or symptoms thereof can include myocardial infarction, stroke, atrial fibrillation, or calcific aortic valve stenosis. A CVD or symptoms thereof include cardiac arrest or peripheral arterial disease.

[0041] The term “lipid disorder” refers to a disorder or a condition that increase levels of LDLs, triglycerides, or both. For example, the lipid disorder can be hyperlipidemia or hypercholesterolemia.

[0042] The term “low-density lipoprotein (LDL),” as used herein, refers to a microscopic blob made up of an outer rim of lipoprotein and a cholesterol center. LDL can have a highly hydrophobic core composed of a polyunsaturated fatty acid known as linoleate and hundreds to thousands esterified and unesterified cholesterol molecules. The core of LDL can also carry triglycerides and other fats and can be surrounded by a shell of phospholipids and unesterified cholesterol.

[0043] As used herein, the term “treat,” “treating” or “treatment” of any disease or disorder refers, in one instance, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another instance, “treat,” “treating” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another instance, “treat,” “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both.

[0044] The terms “prevent,” “preventing,” and “prevention,” as used herein, refer to a decrease in the occurrence of pathology of a condition in a subject, who does not have, but is at risk of or susceptible to developing a disease or condition. The prevention may be complete, e.g., the total absence of pathology of a condition in a subject. The prevention may also be partial, such that the occurrence of pathology of a condition in a subject is less than that which would have occurred without the present disclosure.

[0045] “Administering” and its grammatical equivalents as used herein can refer to providing pharmaceutical compositions described herein to a subject or a patient. Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the composition to the subject, depending upon the type of disease to be treated or the site of the disease. For example, the composition can be administered, e.g., orally, parenterally, by inhalation spray, topically,

rectally, nasally, buccally, vaginally, via an implanted reservoir, or via infusion. One or more such routes can be employed.

[0046] The terms “pharmaceutical composition” and its grammatical equivalents as used herein can refer to a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with one or more pharmaceutically acceptable excipients, carriers, and/or a therapeutic agent to be administered to a subject, *e.g.*, a human in need thereof.

[0047] The term “pharmaceutically acceptable” and its grammatical equivalents as used herein can refer to an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use. “Pharmaceutically acceptable” can refer to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, *i.e.*, the material may be administered to a subject without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the pharmaceutical composition in which it is contained.

[0048] A “pharmaceutically acceptable excipient” refers to an excipient that can be administered to a subject, together with an agent, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the agent.

[0049] The term “therapeutic agent” can refer to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect. Therapeutic agents can also be referred to as “actives” or “active agents.” Such agents include, but are not limited to, cytotoxins, radioactive ions, chemotherapeutic agents, small molecule drugs, proteins, and nucleic acids.

[0050] It is appreciated that certain features of the polynucleic acid molecules, and/or polynucleic acid molecule conjugates, pharmaceutical composition comprising the polynucleic acid molecules or the polynucleic acid molecule conjugates, methods and other aspects, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the polynucleic acid molecules, and/or polynucleic acid molecule conjugates, pharmaceutical composition comprising the polynucleic acid molecules or the polynucleic acid molecule conjugates, methods and other aspects, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace operable processes and/or compositions. In addition, all sub-combinations listed in the embodiments describing such

variables are also specifically embraced by the present polynucleic acid molecules, and/or polynucleic acid molecule conjugates, pharmaceutical composition comprising the polynucleic acid molecules or the polynucleic acid molecule conjugates, methods and other aspects and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

Polynucleic Acid Molecules

Target Regions of Polynucleic Acid Molecules

[0051] Described herein is a polynucleic acid molecule for modulating expression of Lp(a) gene. In some instances, the polynucleic acid molecule is a single-stranded nucleic acid molecule. In some instances, the polynucleic acid molecule is a double-stranded nucleic acid molecule.

[0052] In some aspects, the polynucleic acid molecule described herein hybridizes to certain regions of human Lp(a) mRNA. In some instances, the polynucleic acid molecule comprises a sense strand and an antisense strand, and wherein the antisense strand hybridizes to a certain region of Lp(a) mRNA. As used herein, the term “sense strand” can be interchangeably used with the term “passenger strand”, and the term “antisense strand” can be interchangeably used with the term “guide strand”.

[0053] In some aspects, the polynucleic acid molecule described herein hybridizes to the 5' UTR region of human Lp(a) mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to the coding region of human Lp(a) mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to the 3' UTR region of human Lp(a) mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to a portion of exon 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, or 39 of human Lp(a) mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to a coding region of human Lp(a) mRNA (NCBI Reference Sequence: NM_005577.4).

[0054] In some aspects, the starting position of the binding site of the polynucleic acid molecule described herein on human Lp(a) mRNA (NCBI Reference Sequence: NM_005577.4) is between position 190-210, 250-270; 360-390; 400-450; 460-520, 530-550, 1100-1200, 2600-2700, 2700-2800, 2800-2900, 3000-3300; 3300-3600, 3600-4000, 4000-4200, 4400-4700, 4700-5000, 5000-5200, or 5500-6000.

[0055] The starting position of the binding site of the polynucleic acid molecule described herein on human Lp(a) mRNA (NCBI Reference Sequence: NM_005577.4) can be between position 200-210, 380-390, 410-420, 1100-1200, 2700-2800, 3200-3300, or 3300-3400.

[0056] The starting position of the binding site of the polynucleic acid molecule described herein on human Lp(a) mRNA (NCBI Reference Sequence: NM_005577.4) can be between position 200-210, 250-260, 380-390, 410-430, 430-440, 460-470, 490-500, 500-510, 540-550, 1150-1180, 2650-2700, 2700-2750, 2760-2770, 2850-2900, 3200-3250, 3250-3300, 3300-3310, 3700-3750, 3750-3800, 3950-4000, 4800-4850, 5100-5150, 5500-5550, 5850-5900, or 2750-2800.

Structure of Polynucleic Acid Molecules

[0057] Described herein is a polynucleic acid molecule for modulating expression of Lp(a) gene. In some instances, the polynucleic acid molecule is a single-stranded nucleic acid molecule, wherein the single-stranded nucleic acid molecule is reverse complementary to a target region of Lp(a) mRNA.

[0058] In some aspects, the polynucleic acid molecule described herein is not 100% complementary to the target region of Lp(a) mRNA. Accordingly, in some instances, the polynucleic acid molecule described herein is about 95% complementary to the target region of Lp(a) mRNA. In some instances, the polynucleic acid molecule described herein is about 90% complementary to the target region of Lp(a) mRNA. In some instances, the polynucleic acid molecule described herein is about 85% complementary to the target region of Lp(a) mRNA. In some instances, the polynucleic acid molecule described herein is about 80% complementary to the target region of Lp(a) mRNA. In some instances, the polynucleic acid molecule described herein is about 75% complementary to the target region of Lp(a) mRNA. In some instances, the polynucleic acid molecule described herein is about 70% complementary to the target region of Lp(a) mRNA.

[0059] In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence in Table 1, Table 2 or Table 5. In some instances, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% complementary to a sequence in Table 1, Table 2, or Table 5. In some instances, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% complementary to a nucleic acid sequence selected from SEQ ID NOs: 309-462. In some instances, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% complementary to a nucleic acid sequence selected from SEQ ID NOs: 1-154.

[0060] In some instances, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% complementary to a sequence in Table 1, Table 2, and Table 5, excluding overhangs. In some instances, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% complementary to a nucleic acid sequence selected from

SEQ ID NOs: 309-462, excluding overhangs. In some instances, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% complementary to a nucleic acid sequence selected from SEQ ID NOs: 1-154, excluding overhangs.

[0061] In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 15 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 15 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 16 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 16 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 17 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 17 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 18 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 18 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 19 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the

polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 19 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 20 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 20 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 21 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 21 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 22 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 22 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 with no more than 1, 2, 3, or 4 mismatches.

[0062] In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 15 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 16 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 17 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 18 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 19 consecutive nucleotides that are complementary

to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 20 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 21 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 22 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 with no more than 1, 2, 3, or 4 mismatches.

[0063] In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14, 15, 16, 17, 18, 19, 20, 21, or 22 consecutive nucleotides that are complementary to a sequence in Table 1, Table 2, and Table 5 without overhangs with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14, 15, 16, 17, 18, 19, 20, 21, or 22 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 309-462 without overhangs with no more than 1, 2, 3, or 4 mismatches. In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14, 15, 16, 17, 18, 19, 20, 21, or 22 consecutive nucleotides that are complementary to a nucleic acid sequence of SEQ ID NO: 1-154 without overhangs with no more than 1, 2, 3, or 4 mismatches.

[0064] In some aspects, the polynucleic acid molecule described herein comprises a strand of at least 10, 11, 12, 13, 14, or 15 nucleotides in length. In some aspects, the polynucleic acid molecule described herein comprises a strand of about 15-40, 16-30, 17-30, 18-30, 18-27, 18-25, 18-23, 19-23, 20-23, or 21-23 nucleotides in length. In some aspects, the polynucleic acid molecule described herein comprises a strand of about 15, 16, 17, 18, 19, 20 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a strand of about 21, 22, 23, 24, 25 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a strand of about 26, 27, 28, 29, 30 nucleotides long.

[0065] In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of at least 10, 11, 12, 13, 14, or 15 nucleotides in length. In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of about 15-30, 16-30, 17-30, 18-30, 18-27, 18-25, 18-23, 19-23, 20-23, or 21-23 nucleotides in length. In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of about 15, 16, 17, 18, 19, 20 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of about 21, 22, 23, 24, 25

nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of about 26, 27, 28, 29, 30 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of about 21 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a single-stranded nucleic acid of about 23 nucleotides long.

[0066] In some instances, the polynucleic acid molecule is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand, and wherein the antisense strand is at least partially reverse complementary to a target region of Lp(a) mRNA.

[0067] In some aspects, the antisense strand described herein is not 100% complementary to a target region of Lp(a) mRNA. Accordingly, in some instances, the antisense strand described herein is 100% complementary to a target region of Lp(a) mRNA. In some aspects, the antisense strand described herein is about 95% complementary to a target region of Lp(a) mRNA. In some aspects, the antisense strand described herein is about 90% complementary to a target region of Lp(a) mRNA. In some aspects, the antisense strand described herein is about 85% complementary to a target region of Lp(a) mRNA. In some aspects, the antisense strand described herein is about 80% complementary to a target region of Lp(a) mRNA. In some aspects, the antisense strand described herein is about 75% complementary to a target region of Lp(a) mRNA. In some aspects, the antisense strand described herein is about 70% complementary to a target region of Lp(a) mRNA.

[0068] In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence in Table 1 or Table 2. In other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence in Table 1 or Table 2. In some instances, the sense strand described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, or at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs:309-462. In some instances, the antisense strand described herein comprises a nucleic acid sequences that is at least 80%, at least 85%, at least 90%, or at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs:1-154. In some instances, the sense strand described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406. In some instances, the antisense strand described herein comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, identical to a nucleic acid sequence selected from SEQ ID NOs: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98.

[0069] In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 15 consecutive sequences of the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 15 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 15 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet still other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 16 consecutive sequences out of the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 16 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 16 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet still other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 17 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 17 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 17 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 18 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 18 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 18 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 19 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 19 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 19 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic

acid molecule described herein comprises a nucleic acid sequence comprising at least 20 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 20 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 20 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 21 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 21 consecutive sequences from SEQ ID NOs: 309-462 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 21 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 22 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 22 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In specific aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 23 consecutive sequences from SEQ ID NOs: 1-154 with no more than 1, 2, 3, or 4 mismatches. In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising at least 23 consecutive sequences from the sequences in Table 1 or Table 2 with no more than 1, 2, 3, or 4 mismatches. As used herein, the term “consecutive sequence” refers to a sequence contains a number of consecutive nucleotides from a reference sequence. For example, if a reference sequence is N₁N₂N₃N₄N₅N₆N₇, a consecutive sequence can be N₁N₂N₃N₄ or N₃N₄N₅N₆, but a sequence of N₁N₃N₄N₅ or N₃N₄N₇ cannot be a consecutive sequence.

[0070] In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 15 consecutive sequences of SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 15 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 16 consecutive sequences of SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2, 3 or 4 mismatches. In

some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 16 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 17 consecutive sequences of SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 17 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 18 consecutive sequences of SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2 or 3 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 18 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 19 consecutive sequences of SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2 or 3 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 19 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2 or 3 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 20 consecutive sequences from SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2 or 3 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 20 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2 or 3 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising at least 21 consecutive sequences of SEQ ID NO: 312-314, 319, 326, 329, 352, 355, 357, 368, 372, 396-398, and 406 with no more than 1, 2 or 3 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 21 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2 or 3 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 22 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2 or 3 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising at least 23 consecutive sequences of SEQ ID NO: 4-6, 11, 18, 21, 44, 47, 49, 60, 64, 88-90, and 98 with no more than 1, 2 or 3 mismatches.

[0071] In some aspects, the polynucleic acid molecule described herein comprises a sense and an antisense strand of at least 10, 11, 12, 13, 14, or 15 nucleotides in length. In some aspects, the polynucleic acid molecule described herein comprises a sense and an antisense strand of about 15-30, 16-30, 17-30, 18-30, 18-27, 18-25, 18-23, 19-23, 20-23, or 21-23 nucleotides in length. In some aspects, the polynucleic acid molecule described herein comprises a sense and an antisense strand of about 15, 16, 17, 18, 19, 20 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a sense and an antisense strand of about 21, 22, 23, 24, 25 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a sense and an antisense strand of about 26, 27, 28, 29, 30 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a sense strand of 19 nucleotides long, and an antisense strand of about 21 nucleotides long. In some aspects, the polynucleic acid molecule described herein comprises a sense strand of 21 nucleotides long, and an antisense strand of about 23 nucleotides long.

[0072] In some aspects, the sense strand and the antisense strand described herein are reverse complementary to each other and form a duplex with a 3' overhang on the antisense strand. In some aspects, the sense strand and the antisense strand described herein are reverse complementary to each other and form a duplex with a 5' overhang on the antisense strand. In some aspects, the sense strand and the antisense strand described herein are reverse complementary to each other and form a duplex with a 3' overhang on the sense strand. In some aspects, the sense strand and the antisense strand described herein are reverse complementary to each other and form a duplex with a 5' overhang on the sense strand.

Modifications of Polynucleic Acid Molecules

[0073] In some aspects, described herein is the polynucleic acid molecule described herein with modifications. In some aspects, the modifications described herein occurs one or more different structures of the polynucleic acid molecule described herein (*e.g.*, modifications on sugar ring(s), backbone(s), base(s)). In some aspects, the modifications described herein comprise substitutions of one or more nucleotide in the polynucleic acid molecule described herein. In some aspects, different percentages of the polynucleic acid molecule described herein comprise the modifications described herein. In some aspects, different positions of the polynucleic acid molecule described herein comprise the modifications described herein. WO/2018/035380 is herein incorporated by reference in its entirety.

Types of modifications

[0074] In some aspects, the polynucleic acid molecule described herein comprises one or more sugar-modified nucleotide. In some instances, the sugar-modified nucleotide includes a modification at a 2' hydroxyl group of the ribose moiety. In some instances, the sugar-modified nucleotide includes modification with an H, OR, R, halo, SH, SR, NH₂, NHR, NR₂, or CN, wherein R is an alkyl moiety. In some aspects, the sugar-modified nucleotide is a 2'-fluoro modified nucleotide. In some aspects, the sugar-modified nucleotide is a 2'-O-methyl modified nucleotide or a 2'-alkoxy modified nucleotide (*e.g.*, 2'-methoxy modified nucleotide). In some instances, 2' hydroxyl group modification includes 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA). In some instances, the alkyl moiety comprises a hetero substitution. In some instances, the carbon of the heterocyclic group is substituted by a nitrogen, oxygen or sulfur. In some instances, the heterocyclic substitution includes morpholino, imidazole, and pyrrolidino.

[0075] In some instances, 2' hydroxyl group of the ribose moiety includes a locked or bridged ribose modification (*e.g.*, LNA), an unlocked ribose modification (*e.g.*, UNA), or ethylene nucleic acids (ENA).

[0076] In some aspects, the sugar-modified nucleotide is a 2'- amino modified nucleotide. In some aspects, the sugar-modified nucleotide is a 2'- azido modified nucleotide. In some aspects, the sugar-modified nucleotide is a 2'- deoxy modified nucleotide. In some aspects, the sugar-modified nucleotide is a 2'-O-methoxyethyl (2'-MOE). In some aspects, the sugar-modified nucleotide is a locked nucleic acid (LNA). In some aspects, the sugar-modified nucleotide is an ethylene-bridged nucleic acid (ENA). In some aspects, the sugar-modified nucleotide is a (S)-constrained ethyl (cEt). In some aspects, the sugar-modified nucleotide is a tricyclo-DNA (tcDNA). In some aspects, the sugar-modified nucleotide is a 2'-NH₂ nucleic acid.

[0077] In some aspects, the polynucleotide acid molecule described herein comprises one or more sugarphosphate-modified nucleotide. In some aspects, the modified sugarphosphate is phosphorodiamidate morpholino (PMO). In some aspects, the modified sugarphosphate is phosphoramidate. In some aspects, the modified sugarphosphate is thiophosphoramidate. In some aspects, the modified sugarphosphate is peptide nucleic acid (PNA).

[0078] In some aspects, the polynucleic acid molecule described herein comprises one or more backbone-modified nucleotide. In some aspects, the modified backbone is phosphorothioate. In some aspects, the modified backbone is methylphosphonate. In some aspects, the modified backbone is guanidinopropyl phosphoramidate. In some aspects, the modified backbone is a mesyl-

phosphoramidate (MsPA) linkages. In some instances, the modified backbone comprises one or more of phosphorodithioates, methylphosphonates, 5'-alkylenephosphonates, 5'-methylphosphonate, 3'-alkylene phosphonates, borontrifluoridates, borano phosphate esters and selenophosphates of 3'-5' linkage or 2'-5' linkage, phosphotriesters, thionoalkylphosphotriesters, hydrogen phosphonate linkages, alkyl phosphonates, alkylphosphonothioates, arylphosphonothioates, phosphoroselenoates and phosphoramidates.

[0079] In some aspects, the modified nucleotide comprises a modified guanine (e.g., inosine) or one or more of any types of unnatural nucleic acids.

[0080] In some aspects, the modified backbone is phosphorothioate, and the phosphorothioate is a stereochemically enriched phosphorothioate. In certain aspects, the strand contains at least one stereochemically enriched phosphorothioate. In some aspects, the strand comprises at least 1, 2, 3 stereochemically enriched phosphorothioates. In some aspects, the strand comprises only 1, 2, 3, or 4 stereochemically enriched phosphorothioates. In further aspects, at least one (e.g., one or two) stereochemically enriched phosphorothioate is disposed between two consecutive nucleosides that are two of six 5'-terminal nucleosides of the strand. In yet further aspects, at least one (e.g., one or two) stereochemically enriched phosphorothioate is disposed between two consecutive nucleosides that are two of six 3'-terminal nucleosides of the strand. In still further aspects, one stereochemically enriched phosphorothioate is covalently bonded to the first nucleoside and the second nucleoside from the 5'-end within the strand. In some aspects, one stereochemically enriched phosphorothioate is covalently bonded to the twenty first nucleoside and the twenty second nucleoside from the 5'-end within the strand. In certain aspects, one stereochemically enriched phosphorothioate is covalently bonded to the twenty second nucleoside and the twenty third nucleoside from the 5'-end within the strand. In particular aspects, the stereochemically enriched phosphorothioate has R_P stereochemical identity. In certain aspects, the stereochemically enriched phosphorothioate has S_P stereochemical identity.

[0081] In some aspects, the polynucleotide molecules described herein comprises one or more (e.g., from 1 to 20, from 1 to 10, or from 1 to 5) stereochemically enriched (e.g., internucleoside) phosphorothioates (e.g., having diastereomeric excess of at least 10%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, e.g., up to about 99%, for the P-stereogenic center). The polynucleotide molecules described herein comprises one or more (e.g., from 1 to 20, from 1 to 10, or from 1 to 5; e.g., internucleoside) phosphorodithioates. The phosphorodithioates may be non-P-stereogenic in the polynucleotide molecules described herein. Phosphorothioates and phosphorodithioates may enhance the stability of the polynucleotide molecules described herein to exonuclease activity of serum. Non-P-stereogenic phosphorodithioates may simplify the synthesis

of the polynucleotide molecule described herein by reducing the number of possible diastereomers. Typically, the phosphorothioate or phosphorodithioate may connect two contiguous nucleosides within the six 3'-terminal nucleosides and the six 5'-terminal nucleosides of the polynucleotide molecules described herein. In some aspects, the stereochemically enriched phosphorothioate (e.g., *R_P*-enriched phosphorothioate) may be covalently bonded to the first nucleoside (e.g., the 3'-carbon atom of the first nucleoside) and the second nucleoside (e.g., the 5'-carbon atom of the second nucleoside) from the 5'-end of the antisense strand. Additionally or alternatively, the stereochemically enriched phosphorothioate (e.g., *S_P*-enriched phosphorothioate) may be covalently bonded to the 21st nucleoside (e.g., the 3'-carbon atom of the 21st nucleoside) from the 5'-end and the 22nd nucleoside (e.g., the 5'-carbon atom of the 22nd nucleoside) of the antisense strand. Further, additionally or alternatively, the stereochemically enriched phosphorothioate (e.g., *S_P*-enriched phosphorothioate or *R_P*-enriched phosphorothioate) may be covalently bonded to the 22nd nucleoside (e.g., the 3'-carbon atom of the 22nd nucleoside) and the 23rd nucleoside (e.g., the 5'-carbon atom of the 23rd nucleoside) from the 5'-end of the antisense strand.

[0082] Combinations of a 5' *R_P*-enriched phosphorothioate (e.g., *R_P*-enriched phosphorothioate covalently bonded to the first nucleoside (e.g., the 3'-carbon atom of the first nucleoside) and the second nucleoside (e.g., the 5'-carbon atom of the second nucleoside) from the 5'-end and a 3' *S_P*-enriched phosphorothioate (e.g., *S_P*-enriched phosphorothioate covalently bonded to the 21st nucleoside (e.g., the 3'-carbon atom of the 21st nucleoside) and the 22nd nucleoside (e.g., the 5'-carbon atom of the 22nd nucleoside) from the 5'-end in an antisense strand can produce superior efficacy and/or duration of action, e.g., as measured by the reduction in the activity of the target relative to a reference guide strand that lacks the combination of a 5' *R_P*-enriched phosphorothioate and a 3' *S_P*-enriched phosphorothioate, or a 5' *R_P*-enriched phosphorothioate and a 3' *S_P* and *R_P*-enriched phosphorothioate. In some embodiments, the stereochemically enriched phosphorothioate may comprise *R_PR_PS_PS_P* (*R_PR_P* at the positions 1 and 2 of the guide strand and *S_PS_P* at the positions 21 and 22 of the guide strand) or *R_PR_PS_PR_P* (*R_PR_P* at the positions 1 and 2 of the guide strand and *S_PR_P* at the positions 21 and 22 of the guide strand). In some aspects, the polynucleotide molecules described herein comprises four stereochemically enriched phosphorothioates: (1) a *R_P*-enriched phosphorothioate covalently bonded to the 1st nucleoside (e.g., the 3'-carbon atom of the 1st nucleoside) and the 2nd nucleoside (e.g., the 5'-carbon atom of the 2nd nucleoside) from the 5'-end of the antisense strand; (2) a *R_P*-enriched phosphorothioate covalently bonded to the 2nd nucleoside (e.g., the 3'-carbon atom of the 2nd nucleoside) and the 3rd nucleoside (e.g., the 5'-carbon atom of the 3rd nucleoside) from the 5'-end of the antisense strand; (3) a *S_P*-enriched phosphorothioate covalently bonded to the 21st nucleoside (e.g., the 3'-carbon atom of the 21st nucleoside) and the

22th nucleoside (e.g., the 5'-carbon atom of the 22th nucleoside) from the 5'-end of the antisense strand; and (4) a Sp-enriched phosphorothioate covalently bonded to the 22th nucleoside (e.g., the 3'-carbon atom of the 22th nucleoside) and the 23rd nucleoside (e.g., the 5'-carbon atom of the 23rd nucleoside) from the 5'-end of the antisense strand. In some aspects, the polynucleotide molecules described herein comprises four stereochemically enriched phosphorothioates: (1) a Rp-enriched phosphorothioate covalently bonded to the 1st nucleoside (e.g., the 3'-carbon atom of the 1st nucleoside) and the 2nd nucleoside (e.g., the 5'-carbon atom of the 2nd nucleoside) from the 5'-end of the antisense strand; (2) a Rp-enriched phosphorothioate covalently bonded to the 2nd nucleoside (e.g., the 3'-carbon atom of the 2nd nucleoside) and the 3rd nucleoside (e.g., the 5'-carbon atom of the 3rd nucleoside) from the 5'-end of the antisense strand; (3) a Sp-enriched phosphorothioate covalently bonded to the 21st nucleoside (e.g., the 3'-carbon atom of the 21st nucleoside) and the 22th nucleoside (e.g., the 5'-carbon atom of the 22th nucleoside) from the 5'-end of the antisense strand; and (4) a Rp-enriched phosphorothioate covalently bonded to the 22th nucleoside (e.g., the 3'-carbon atom of the 22th nucleoside) and the 23rd nucleoside (e.g., the 5'-carbon atom of the 23rd nucleoside) from the 5'-end of the antisense strand.

[0083] In some aspects, the polynucleotide molecule described herein comprises one or more purine modification. In some aspects, the purine modification described herein is 2,6-diaminopurine. In some aspects, the purine modification described herein is 3-deaza-adenine. In some aspects, the purine modification described herein is 7-deaza-guanine. In some aspects, the purine modification described herein is 8-azido-adenine.

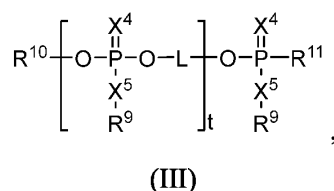
[0084] In some aspects, the polynucleotide molecule described herein comprises one or more pyrimidine modification. In some aspects, the pyrimidine modification described herein is 2-thio-thymidine. In some aspects, the pyrimidine modification described herein is 5-carboxamide-uracil. In some aspects, the pyrimidine modification described herein is 5-methyl-cytosine. In some aspects, the pyrimidine modification described herein is 5-ethynyl uracil.

[0085] In some cases, the polynucleic acid molecule described herein comprises an abasic substitution. In those cases where a hybridized polynucleotide construct is contemplated for use as siRNA, a reduction of miRNA-like off-target effects is desirable. The inclusion of one or more (e.g., one or two) abasic substitutions in the hybridized polynucleotide constructs may reduce or even eliminate miRNA-like off-target effects, as the abasic substitutions lack nucleobases that are capable of engaging in base-pairing interactions and alleviate steric hindrance. Thus, the polynucleotide molecule disclosed herein may include one or more (e.g., one or two) abasic substitutions. In some aspects, abasic substitution is at the 5th nucleotide from the 5' end of the

antisense strand described herein. In some aspects, abasic substitution is at the 7th nucleotide from the 5' end of the antisense strand described herein.

[0086] When the polynucleotide molecule disclosed herein includes two or more of the abasic substitutions, their structures may be same or different. In certain aspects, a sense strand contains one abasic substitution (e.g., an antisense strand may be free of abasic substitutions). In other aspects, an antisense strand contains one abasic substitution (e.g., a sense strand may be free of abasic substitutions). In yet other aspects, an antisense strand contains one abasic substitution, and a sense strand contains one abasic substitution. In further aspects, a sense strand includes an abasic substitution between a nucleoside number (x) and a nucleoside number (x+1), where x is an integer from 2 to 7. In yet further aspects, an antisense strand includes an abasic substitution between a nucleoside number (x) and a nucleoside number (x+1), where x is an integer from 2 to 7.

[0087] The abasic substitution may be of formula (III):



where

L is a sugar analogue, or is substituted with a heteroacyl from A, U, C, G, or is any other substituted nucleic acid (e.g., locked or unlocked nucleic acid, glycol nucleic acid, etc.);

each X⁴ is independently O or S;

each X⁵ is independently O, S, NH, or a bond;

each R⁹ is independently H, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted (C₁₋₉ heterocyclyl)-C₁₋₆-alkyl, optionally substituted (C₆₋₁₀ aryl)-C₁₋₆-alkyl, optionally substituted (C₃₋₈ cycloalkyl)-C₁₋₆-alkyl, –LinkA(–T)_p, or a conjugation moiety;

each LinkA is independently a multivalent linker (e.g., including –C(O)–N(H)–);

each T is independently an auxiliary moiety;

R¹⁰ is a bond to a 3'-carbon atom of a nucleoside (x) in the strand;

R¹¹ is a bond to a 5'-oxygen atom of a nucleoside (x+1) in the strand;

p is an integer from 1 to 6; and

t is an integer from 1 to 6.

[0088] In some aspects, the abasic substitution described herein is attached to the antisense strand of the polynucleic acid molecule described herein. In particular aspects, an abasic substitution (e.g., an internucleotide, abasic spacer of formula (III) in which t is 1) may be included in the

antisense strand described herein (e.g., within the seed region of the guide strand). In some aspects, an abasic substitution (e.g., an internucleotide, abasic spacer of formula (III) in which t is 1) may be bonded to the 3' carbon atom of the second, third, fourth, or fifth nucleoside from the 5'-end of the antisense strand described herein. In certain aspects, an abasic substitution (e.g., an internucleotide, abasic spacer of formula (III) in which t is 1) may be bonded to the 3' carbon atom of the thirteenth, fourteenth, fifteenth, or sixteenth nucleoside from the 5'-end of the antisense strand described herein. In some aspects, an abasic substitution fourth, fifth, sixth, seventh, eighth, and/or ninth nucleoside from the 5'-end of the antisense strand described herein.

[0089] The polynucleotide molecule described herein may contain a strand including a seed region including a hypoxanthine nucleobase-containing nucleoside (e.g., inosine).

[0090] In certain aspects, the hypoxanthine nucleobase-containing nucleoside is a second nucleoside from the 5'-end in the strand. In further aspects, the hypoxanthine nucleobase-containing nucleoside is a third nucleoside from the 5'-end in the strand. In yet further aspects, the hypoxanthine nucleobase-containing nucleoside is a fourth nucleoside from the 5'-end in the strand. In still further aspects, the hypoxanthine nucleobase-containing nucleoside is a fifth nucleoside from the 5'-end in the strand. In particular aspects, the hypoxanthine nucleobase-containing nucleoside is a sixth nucleoside in the strand. In particular aspects, the hypoxanthine nucleobase-containing nucleoside is a seventh nucleoside in the strand.

[0091] The Amount and Location of Modifications

[0092] In some aspects, the polynucleotide molecule described herein comprises one or more type of modifications as described above. Accordingly, in some aspects, about 10% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 20% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 30% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 40% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 50% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 60% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 70% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, about 80% of the nucleotides from the polynucleotide molecule

described herein are modified with one or more type of modifications as described above. In other aspects, about 90% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above. In other aspects, 100% of the nucleotides from the polynucleotide molecule described herein are modified with one or more type of modifications as described above.

[0093] In some aspects, the one or more types of modifications described herein occurs in the seed region within the the polynucleotide molecule described herein. In some aspects, the one or more types of modifications described herein occurs at different positions within the polynucleotide molecule described herein. In specific aspects, the one or more types of modifications described herein occurs at 3' terminal of the polynucleotide molecule described herein. In specific aspects, the one or more types of modifications described herein occurs at 5' terminal of the polynucleotide molecule described herein. In specific aspects, the one or more types of modifications described herein occurs dispersedly within the polynucleotide molecule described herein. In specific aspects, the one or more types of modifications described herein occurs in clusters within the polynucleotide molecule described herein.

Specific Modification Patterns

[0094] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises about three 2'-fluoro modified nucleotides and about eighteen 2'-O-methyl modified nucleotides, and wherein the antisense strand comprises about five 2'-fluoro modified nucleotides and about eighteen 2'-O-methyl modified nucleotides.

[0095] In some aspects, described herein is a polynucleic acid modified with a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'- nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', wherein n stands for a 2'-O-methyl modified nucleotide, and wherein Nf stands for a 2'-fluoro modified nucleotide. In some aspects, the sense strand comprises '5- NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises '5-nNfnNfnNfnNfnNfnnnNfnNfnNfnNfnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the sense strand comprises '5-nnnnnnNfnNfnNfnnnnnnnnn -3', wherein the antisense strand comprises '5-nNfnnnnNfnNfnNfnnnnNfnNfnnnnnnn -3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the sense strand comprises '5-nnnnnnnnNfnNfnnnnnnnnnnn -3', wherein the antisense strand comprises '5-nNfnnnnnnnnnNfnNfnnnnnnnnn -3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the sense strand comprises '5-nnnnnnNfnNfnNfnnnnnnnnn -3', wherein the

antisense strand comprises '5-nNfnnnnnnnnnNfnNfnNfnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some instances, each modification pattern includes one or more phosphorothioate internucleotide linkages in locations such as between 1st and 2nd nucleotides on 5' end, between 2nd and 3rd nucleotides on 5' end, between 1st and 2nd nucleotides on 3' end, and/or between 2nd and 3rd nucleotides on 3' end.

[0096] In some aspects, the antisense strand comprises 5'-nNfnnnnNfnNfNfnnnnNfnNfnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the antisense strand comprises 5'-nNfnnnnNfnnnnnnnnNfnNfnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the antisense strand comprises 5'-nNfnnnnNfnnnnNfnNfnnnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the antisense strand comprises or consists of two 2'-fluoro modified nucleotides at positions 2 and 14, respectively. In some aspects, the antisense strand comprises or consists of three 2'-fluoro modified nucleotides at positions 2, 12, and 14, respectively. In some aspects, the antisense strand comprises or consists of three 2'-fluoro modified nucleotides at positions 2, 14, and 16, respectively. In some aspects, the antisense strand comprises or consists of four 2'-fluoro modified nucleotides at positions 2, 12, 14, and 16, respectively. In some aspects, the antisense strand comprises a 2'-fluoro modified nucleotide at position 6, 7, 8, or 9. In some aspects, the antisense strand comprises a 2'-fluoro modified nucleotide at position 4. In some aspects, the antisense strand does not contain a 2'-fluoro modified nucleotide at position 4.

[0097] In some aspects, the sense strand comprises 5'-nnnnnnNfNfNfnnnnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the sense strand comprises 5'- nnnnnnNfNfNfNfnnnnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the sense strand comprises 5'-nnnnnnnnNfNfNfnnnnnnnnnn-3', wherein Nf stands for a 2'-fluoro modified nucleotide, and wherein n stands for a 2'-O-methyl modified nucleotide. In some aspects, the sense strand comprises or consists of two 2'-fluoro modified nucleotides at positions 9 and 11, respectively. In some aspects, the sense strand comprises or consists of three 2'-fluoro modified nucleotides at positions 7, 9 and 11, respectively. In some aspects, the sense strand comprises or consists of three 2'-fluoro modified nucleotides at positions 9, 10 and 11, respectively. In some aspects, the sense strand comprises or consists of four 2'-fluoro modified nucleotides at positions 7, 9, 10 and 11, respectively. In some aspects, the sense

strand comprises a 2'-fluoro modified nucleotide at position 8, 12, or 16. In some aspects, the sense strand does not contain a 2'-fluoro modified nucleotide at position 8, 12, or 16.

[0098] In some aspects, described herein is a specific modification pattern for the polynucleic acid molecule which is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand. In some aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 2 from the 5' end. In some aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 14 from the 5' end. In some aspects, the antisense strand comprises 2'-fluoro modified nucleotides in positions 2 and 14 from the 5' end. In some aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 12 from the 5' end. In some aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 16 from the 5' end. In other aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 6 from the 5' end. In other aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 7 from the 5' end. In other aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 8 from the 5' end. In other aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 9 from the 5' end. In other aspects, the antisense strand comprises a 2'-fluoro modified nucleotide in position 4 from the 5' end.

[0099] In some aspects, described herein is a specific modification pattern for the polynucleic acid molecule which is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand. In some aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 9 from the 5' end. In some aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 11 from the 5' end. In some aspects, the sense strand comprises 2'-fluoro modified nucleotides in positions 9 and 11 from the 5' end. In some aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 7 from the 5' end. In some aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 10 from the 5' end. In some aspects, the sense strand comprises 2'-fluoro modified nucleotides in positions 9, 11, and 7 from the 5' end. In some aspects, the sense strand comprises 2'-fluoro modified nucleotides in positions 9 and 11, and 10 from the 5' end. In some aspects, the sense strand comprises 2'-fluoro modified nucleotides in positions 9 and 7 from the 5' end. In some aspects, the sense strand comprises 2'-fluoro modified nucleotides in positions 9 and 10 from the 5' end. In some aspects, the sense strand comprises 2'-fluoro modified nucleotides in positions 9, 11, 7, and 10 from the 5' end. In other aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 8 from the 5' end. In other aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 12 from the 5' end. In other aspects, the sense strand comprises a 2'-fluoro modified nucleotide in position 16 from the 5' end.

[0100] In some aspects, the sense and antisense strand of the polynucleic acid molecule comprises any combination of two or more 2'-fluoro modified nucleotides at the positions described in the above two paragraphs.

[0101] In some aspects, the antisense strand comprises 5' - nNfnnnNfnNfnfnnnnnNfnNfnnnnnnn-3'. In some aspects, the antisense strand comprises 5' - nNfnnnNfnnnnnnnNfnNfnnnnnnn-3'. In some aspects, the antisense strand comprises 5' - nNfnnnNfnnnnnNfnNfnnnnnnnnn-3'. In the modification patterns described above, "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0102] In some aspects, the sense strand comprises 5'- nnnnnnNfnNfnNfnnnnnnnnn-3'. In some aspects, the sense strand comprises 5'- nnnnnnNfnNfnNfnfnnnnnnnnn-3'. In some aspects, the sense strand comprises 5'- nnnnnnnNfnNfnNfnnnnnnnnn-3'. In the modification patterns described above, "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0103] In some aspects, described herein is a specific modification pattern for the polynucleic acid molecule which is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand, wherein the sense strand comprises about twelve 2'-fluoro modified nucleotides and about nine 2'-O-methyl modified nucleotides, and wherein the antisense strand comprises about nine 2'-fluoro modified nucleotides and about fourteen 2'-O-methyl modified nucleotides.

[0104] In some aspects, described herein is a specific modification pattern, wherein the sense strand is fully modified and comprises twelve 2'-fluoro modified nucleotides, nine 2'-O-methyl modified nucleotides, and wherein the antisense strand is fully modified and comprises nine 2'-fluoro modified nucleotides and fourteen 2'-O-methyl modified nucleotides.

[0105] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5' - NfnNfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises 5' - nNfnNfnNfnNfnNfnnnNfnNfnNfnNfnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0106] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5' - NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises 5' - nNfnNfnNfnNfnNfnnnNfnNfnNfnNfnnn-3', wherein the sense and/or antisense strand comprises one or more phosphorothioate linkage, wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide. In other aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5' - NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises 5' - nNfnNfnNfnNfnNfnnnNfnNfnNfnNfnnn-3', wherein the sense comprises two phosphorothioate

linkages, wherein the antisense comprises four phosphorothioate linkages, wherein “Nf” stands for a 2’-fluoro modified nucleotide, and wherein “n” stands for a 2’-O-methyl modified nucleotide.

[0107] In some aspects, described herein is a specific modification pattern, wherein the sense strand and/or antisense strand is modified as Type I in **Table 8**.

Table 8. Nucleotide Modification Patterns

Pattern Name	Pattern
Type I for sense strand	5’- NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNf-3’
Type I for antisense strand	5’-nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnfsnsn-3’
Type II for sense strand	5’- nsnsnnnnNfnNfnNfnnnnnnnnn -3’
Type II for antisense strand	5’- nsNfsnnnnNfnNfnNfnnnnnNfnNfnnnnsnsn -3’
Type III for sense strand	5’- nsnsnnnnnnNfnNfnnnnnnnnnnn -3’
Type III for antisense strand	5’- nsNfsnnnnnnnnNfnNfnnnnnnnnsnsn -3’
Type IV for sense strand	5’- nsnsnnnnNfnNfnNfnnnnnnnnn -3’
Type IV for antisense strand	5’- nsNfsnnnnnnnnNfnNfnNfnnnnsnsn -3’
Type V for sense strand	5’- nsnsnnnnNfnNfnNfnnnnnnnnn -3’
Type V for antisense strand	5’-nsNfsnnnnNfnnnNfnNfnNfnnnnsnsn -3’
Type VI for sense strand	5’- nnnnnNfnNfnNfnnnnnnnnn-invndN-invndN -3’

Note: “Nf” stands for a 2’-fluoro modified nucleotide, “n” stands for a 2’-O-methyl modified nucleotide, “s” stands for a 3'-phosphorothioate, “invndN” stands for an inverted deoxy-nucleotide.

[0108] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 309-462, an antisense strand comprises a nucleic acid sequence of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in Type I modification pattern specified in **Table 8**.

[0109] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises about four 2’-fluoro modified nucleotides and about seventeen 2’-O-methyl modified nucleotides, and wherein the antisense strand comprises about six 2’-fluoro modified nucleotides and about seventeen 2’-O-methyl modified nucleotides.

[0110] In some aspects, described herein is a specific modification pattern, wherein the sense strand is fully modified and comprises four 2’-fluoro modified nucleotides, seventeen 2’-O-methyl modified nucleotides, and wherein the antisense strand is fully modified and comprises six 2’-fluoro modified nucleotides and seventeen 2’-O-methyl modified nucleotides.

[0111] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5’- nnnnnNfnNfnNfnnnnnnnnn -3’, wherein the antisense strand comprises

5'- nNfnnnNfnNfNfnnnnNfnNfnnnnnnn - 3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0112] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnNfnNfNfNfnnnnnnnnn - 3', wherein the antisense strand comprises 5'- nNfnnnNfnNfNfnnnnNfnNfnnnnnnn - 3', wherein the sense and/or antisense strand comprises one or more phosphorothioate linkage, wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide. In other aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnNfnNfNfNfnnnnnnnnn - 3', wherein the antisense strand comprises 5'- nNfnnnNfnNfNfnnnnNfnNfnnnnnnn - 3', wherein the sense comprises two phosphorothioate linkages, wherein the antisense comprises four phosphorothioate linkages, wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0113] In some aspects, described herein is a specific modification pattern, wherein the sense strand and/or antisense strand is modified as Type II in **Table 8**.

[0114] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 309-462, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in Type II modification pattern specified in **Table 8**.

[0115] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises about two 2'-fluoro modified nucleotides and about nineteen 2'-O-methyl modified nucleotides, and wherein the antisense strand comprises about three 2'-fluoro modified nucleotides and about twenty 2'-O-methyl modified nucleotides.

[0116] In some aspects, described herein is a specific modification pattern, wherein the sense strand is fully modified and comprises two 2'-fluoro modified nucleotides and nineteen 2'-O-methyl modified nucleotides, and wherein the antisense strand is fully modified and comprises three 2'-fluoro modified nucleotides and twenty 2'-O-methyl modified nucleotides.

[0117] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnnNfnNfnnnnnnnnn - 3', wherein the antisense strand comprises 5'- nNfnnnnnnnnNfnNfnnnnnnnnn - 3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0118] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnnNfnNfnnnnnnnnn - 3', wherein the antisense strand comprises 5'- nNfnnnnnnnnNfnNfnnnnnnnnn - 3', wherein the sense and/or antisense strand comprises one or more phosphorothioate linkage, wherein "Nf" stands for a 2'-fluoro modified nucleotide, and

wherein “n” stands for a 2’-O-methyl modified nucleotide. In other aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5’- nnnnnnnNfnNfnnnnnnnnn - 3’, wherein the antisense strand comprises 5’- nNfnnnnnnnnnNfnNfnnnnnnnnn -3’, wherein the sense comprises two phosphorothioate linkages, wherein the antisense comprises four phosphorothioate linkages, wherein “Nf” stands for a 2’-fluoro modified nucleotide, and wherein “n” stands for a 2’-O-methyl modified nucleotide.

[0119] In some aspects, described herein is a specific modification pattern, wherein the sense strand and/or antisense strand is modified as Type III in **Table 8**.

[0120] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 309-462, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in Type III modification pattern specified in **Table 8**.

[0121] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises about three 2’-fluoro modified nucleotides and about eighteen 2’-O-methyl modified nucleotides, and wherein the antisense strand comprises about four 2’-fluoro modified nucleotides and about nineteen 2’-O-methyl modified nucleotides.

[0122] In some aspects, described herein is a specific modification pattern, wherein the sense strand is fully modified and comprises three 2’-fluoro modified nucleotides, eighteen 2’-O-methyl modified nucleotides, and wherein the antisense strand is fully modified and comprises four 2’-fluoro modified nucleotides, nineteen 2’-O-methyl modified nucleotides.

[0123] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5’- nnnnnnNfnNfnNfnnnnnnnnn -3’, wherein the antisense strand comprises 5’- nNfnnnnnnnnnNfnNfnNfnnnnnnn -3’, wherein “Nf” stands for a 2’-fluoro modified nucleotide, and wherein “n” stands for a 2’-O-methyl modified nucleotide.

[0124] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5’- nnnnnnNfnNfnNfnnnnnnnnn -3’, wherein the antisense strand comprises 5’- nNfnnnnnnnnnNfnNfnNfnnnnnnn -3’, wherein the sense and/or antisense strand comprises one or more phosphorothioate linkage, wherein “Nf” stands for a 2’-fluoro modified nucleotide, and wherein “n” stands for a 2’-O-methyl modified nucleotide. In other aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5’- nnnnnnNfnNfnNfnnnnnnnnn -3’, wherein the antisense strand comprises 5’- nNfnnnnnnnnnNfnNfnNfnnnnnnn -3’, wherein the sense comprises two phosphorothioate linkages, wherein the antisense comprises four phosphorothioate linkages, wherein “Nf” stands for a 2’-fluoro modified nucleotide, and wherein “n” stands for a 2’-O-methyl modified nucleotide.

[0125] In some aspects, described herein is a specific modification pattern, wherein the sense strand and/or antisense strand is modified as Type IV in **Table 8**.

[0126] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 309-462, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in Type IV modification pattern specified in **Table 8**.

[0127] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises about three 2'-fluoro modified nucleotides and about eighteen 2'-O-methyl modified nucleotides, and wherein the antisense strand comprises about five 2'-fluoro modified nucleotides and about eighteen 2'-O-methyl modified nucleotides.

[0128] In some aspects, described herein is a specific modification pattern, wherein the sense strand is fully modified and comprises three 2'-fluoro modified nucleotides and eighteen 2'-O-methyl modified nucleotides, and wherein the antisense strand is fully modified and comprises five 2'-fluoro modified nucleotides, eighteen 2'-O-methyl modified nucleotides.

[0129] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0130] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', wherein the sense and/or antisense strand comprises one or more phosphorothioate linkage, wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide. In other aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', wherein the sense comprises two phosphorothioate linkages, wherein the antisense comprises four phosphorothioate linkages, wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

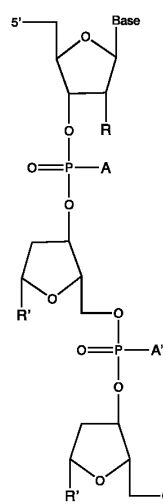
[0131] In some aspects, described herein is a specific modification pattern, wherein the sense strand and/or antisense strand is modified as Type V in **Table 8**.

[0132] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 309-462, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in Type V modification pattern specified in **Table 8**.

[0133] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises about three 2'-fluoro modified nucleotides and about eighteen 2'-O-methyl modified nucleotides, with one or more inverted deoxy-nucleotides on the 3' end as an overhang.

[0134] In some aspects, described herein is a specific modification pattern, wherein the sense strand is fully modified and comprises three 2'-fluoro modified nucleotides and eighteen 2'-O-methyl modified nucleotides, with two inverted deoxy-nucleotides on the 3' end as an overhang.

[0135] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-invN-invN-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, wherein "n" stands for a 2'-O-methyl modified nucleotide, and "invN" stands for an inverted deoxy-nucleotide. In some instances, the invN is an inverted deoxy-thymine. In some aspects, the linker conjugated with one or more targeting moieties as shown in Formula (IV') or (IV'') is added to the first nucleic acid on the 5' end. In some aspects, the linker conjugated with one or more GalNAc as shown in Formula (V') or (V'') is added to the first nucleic acid on the 5' end. In some aspects, the modification pattern comprises one or more phosphorothioate linkages. In some aspects, the modification pattern is shown in Formula (VII). In some aspects, the 5' end modification known in the art is applied to the one or more inverted nucleotides.



herein, in some instances, R is -O-methyl; wherein R' is thymine, abasic, or others; wherein A is -O or -S; and wherein A' is -O or -S.

[0136] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 309-462, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in Type VI modification pattern specified in Table 8.

[0137] In some aspects, the polynucleotide molecule provided herein comprises a single-stranded nucleic acid comprising a nucleic acid sequence selected from one of SEQ ID NOs: 1-154. In some aspects, the polynucleotide molecule provided herein comprises a single-stranded nucleic acid that is complementary to a nucleic acid sequence selected from SEQ ID NOs: 309-462.

[0138] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence selected from one of SEQ ID NOs: 309-462 and an antisense strand comprising a nucleic acid sequence selected from one of SEQ ID NOs: 1-154. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence selected from one of SEQ ID NOs: 309-462, an antisense strand comprising a nucleic acid sequence selected from one of SEQ ID NOs: 1-154, and wherein the sense and/or antisense strand is modified in the modification pattern as described herein.

[0139] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence selected from one of SEQ ID NOs: 463-616, and an antisense strand comprising a nucleic acid sequence selected from SEQ ID NOs: 155-308.

[0140] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usAfsgaugAfccaaGfcUfuGfgcaggsusc (SEQ ID NO: 158) and a sense strand comprising the nucleotide sequence of cscsugccAfaGfcUfuggucaucua (SEQ ID NO: 466), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0141] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usAfsuagaUfgaccAfaGfcUfuggcasgsg (SEQ ID NO: 159) and a sense strand comprising the nucleotide sequence of usgsccaaGfcUfuGfgucaucua (SEQ ID NO: 467), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to

2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0142] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsauagAfuagCfaAfgCfuuggcsasg (SEQ ID NO: 160) and a sense strand comprising the nucleotide sequence of gscscaagCfuUfgGfucaucauga (SEQ ID NO: 468), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0143] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsgacgGfcaguCfcCfuUfcugcgsusc (SEQ ID NO: 165) and a sense strand comprising the nucleotide sequence of csgscagaAfgGfgAfcugccgucga (SEQ ID NO: 473), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0144] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usUfscuagGfcuugGfaAfcCfggggusasa (SEQ ID NO: 172) and a sense strand comprising the nucleotide sequence of ascscgGfuUfcCfaagccuagaa (SEQ ID NO: 480), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0145] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usAfsGCCUCfuaggCfuUfgGfaaccgsgsg (SEQ ID NO: 175) and a sense strand comprising the nucleotide sequence of csgsguucCfaAfgCfcuagaggcua (SEQ ID NO: 483), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0146] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usUfsuaccGfugguAfgCfaCfuccugscsa (SEQ ID NO: 198) and a sense strand comprising the nucleotide sequence of csasggagUfgCfuAfcacgguaaa (SEQ ID NO: 506), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0147] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usUfsguccAfuacCfGfGfuagcascsu (SEQ ID NO: 201) and a sense strand comprising the nucleotide sequence of usgscuacCfaCfGfGfuauggacaa (SEQ ID

NO: 509), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0148] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsucugUfccauUfaCfcGfugguasgsc (SEQ ID NO: 203) and a sense strand comprising the nucleotide sequence of usasccacGfgUfaAfuggacagaga (SEQ ID NO: 511), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0149] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usAfsuuguGfucagGfuUfgCfaguacsusc (SEQ ID NO: 214) and a sense strand comprising the nucleotide sequence of gsusacugCfaAfcCfugacacaaua (SEQ ID NO: 522), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0150] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand

comprising the nucleotide sequence of usUfsgcguCfugagCfaUfuGfugucasgsg (SEQ ID NO: 218) and a sense strand comprising the nucleotide sequence of usgsacacAfaUfgCfucagacgcaa (SEQ ID NO: 526), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0151] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usUfssaacuCfugucCfaUfaAfugguasgsu (SEQ ID NO: 242) and a sense strand comprising the nucleotide sequence of usasccauUfaUfgGfacagaguuaa (SEQ ID NO: 550), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0152] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfscaagCfuuggCfaAfgUfucuucscsu (SEQ ID NO: 243) and a sense strand comprising the nucleotide sequence of gsasagaaCfuUfgCfcaagcuugga (SEQ ID NO: 551), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0153] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usAfsgaugAfccaaGfcUfuGfgcaagsusu (SEQ ID NO: 244) and a sense strand comprising the nucleotide sequence of csusugccAfaGfcUfuggucaucua (SEQ ID NO: 552), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0154] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule an antisense strand comprising the nucleotide sequence of usGfsguccGfacuaUfgCfuGfgugugsgsu (SEQ ID NO: 252) and a sense strand comprising the nucleotide sequence of csascaccAfgCfaUfagucggacca (SEQ ID NO: 560), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0155] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule an antisense strand comprising the nucleotide sequence of usAfsgccuCfuaggCfuUfgGfaaccgsgsg (SEQ ID NO: 175) and a sense strand comprising the nucleotide sequence of csgsguucCfaAfgCfcuagaggcua (SEQ ID NO: 483), wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-

methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0156] Further provided herein is a polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule an antisense strand comprising the nucleotide sequence of usAfsuuguGfucagGfuUfgCfaguacsusc (SEQ ID NO: 214) and a sense strand comprising the nucleotide sequence of gsusacugCfaAfcCfugacacaaaua (SEQ ID NO: 522), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate.

[0157] Table 1.

Compd ID	sIRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	sIRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transf. Ipt
SRS-000023	G-000023	UCCAAGCUTUGGCAGGUCCUUCU	1	usCfbaagCfuuagCfaGfUfcuucacsu	155	P-000023	GAAAGACCUGCCAAAGCUTUGGA	309	gsasaggacCfcUfGcfcaagcuugga	463	198
SRS-000024	G-000024	UACCAAGCUTUGGCAGGUCCUCC	2	usAfbaacaaGfuuagGfcAfGcfuucuuasc	156	P-000024	AAGGACCUGCCAAAGCUTUGGUA	310	asasggacCfcUfGfcfbaagcuuggua	464	199
SRS-000025	G-000025	UAUGACCAAGCUTUGGCAGGUCCU	3	usAfbugacCfbaagUfuGfGcfbaagcuacsu	157	P-000025	GACCTUGCCAAAGCUTUGGUCUA	311	gsascucgCfcAfbaGfcuagcuuaua	465	202
SRS-000026	G-000026	UAGAUGACCAAGCUTUGGCAGGUCC	4	usAfbugaaAfbaacGfcUfuGfbaagcuasc	158	P-000026	CCUUGCCAAAGCUTUGGUCUAUCUA	312	cscsuagcaAfbaGfcUfbugcaucua	466	204
SRS-000027	G-000027	UAUAGAUAGACCAAGCUTUGGCAGG	5	usAfbaugaUfbaacAfbaGfcUfbugcaagsg	159	P-000027	UGCCAAAGCUTUGGUCUAUCUAUA	313	usgsccaaGfcUfuGfbaucuaaua	467	206
SRS-000028	G-000028	UCAUAGAUAGACCAAGCUTUGGCAG	6	usCfbaugaAfbugacCfbaAfbaGcfuuagcaasg	160	P-000028	GCCAAAGCUTUGGUCUAUCUAUGA	314	gsascaagCfcUfuGfbaucuaaua	468	207
SRS-000029	G-000026	UAUCAAGCCAGCAUUTUGGUAU	7	usAfbaucacGfbaagCfbaUfuUfbuguaggsu	161	P-000029	UACCCAAUAGCUTUGGCUUUAUA	315	usascacaAfbaUfGcfbaagcuuga	469	260
SRS-000030	G-000027	UGUCCCTUUCUGCUCUUGAGCAU	8	usGfbaucUfuuagCfcUfuUfbaagcausu	162	P-000030	UGCTUCAGACGACAGAGGGACA	316	usgsucuaGfbaCfcGcfbaagaggaca	470	374
SRS-000031	G-000028	UCGGCAGUCCCTUUCUGCUCUGA	9	usCfbaagcaGfuaccUfuCfbaGfbaagcuagsa	163	P-000031	AGACGCAGAAAGGACUGGCCGA	317	asgsacgcAfbaUfbaGfbaagcuagca	471	379
SRS-000032	G-000029	UGACGGCAGUCCCTUUCUGCGUCU	10	usGfbaagcCfbaagCfcUfuCfbaagcuacsu	164	P-000032	ACGCAGAAAGGACUGCCGUGA	318	asasgcagAfbaGfGfcfbaucgcugca	472	381
SRS-000033	G-000011	UCGACGGCAGUCCCTUUCUGCGUC	11	usCfbaagcGfbaagCfcCfbaUfbaagcuasc	165	P-000033	CGCAGAAAGGACUGCCGUCGA	319	csgscagaAfbaGfGfbaAfbaucgcugca	473	382
SRS-000034	G-000030	UCCGACGGCAGUCCCTUUCUGCGU	12	usCfbaagcGfbaagUfuCfbaUfbaagcuagsu	166	P-000034	GCAGAAAGGACUGCCGUCGCA	320	gsascaagaGfbaGfbaCfbaagcuagca	474	383
SRS-000035	G-000031	UGAACCGGGGUAAACAGUCGAGG	13	usGfbaacGfbaagAfbaCfbaGfbaagcuasg	167	P-000035	UCCGACUGUUAACCCCGUUA	321	usascgacUfbaUfuAfbaGfbaagcuua	475	406
SRS-000036	G-000032	UGGAACCGGGGUAAACAGUCGGAG	14	usGfbaacCfbaagUfuAfbaAfbaGfbaagcuasg	168	P-000036	CCGACUGUUAACCCCGUUA	322	csgsagacGfbaUfuAfbaCfbaagcuua	476	407
SRS-000037	G-000033	UUGGAACCGGGGUAAACAGUCGGA	15	usUfbaagcCfbaagGfbaCfbaGfbaagcuasg	169	P-000037	CGACUGUUAACCCCGGUUA	323	csgsacugUfuAfbaCfbaagcuua	477	408
SRS-000038	G-000034	UGCUTUGGAACCGGGGUAAACAGUC	16	usCfbaagUfbaacGfbaGfbaGfbaagcuasg	170	P-000038	CUGUUAACCCCGGUUA	324	csusgmuacCfcCfcGfbaagcuagca	478	411
SRS-000039	G-000035	UGGCUUGGAACCGGGGUAAACAGU	17	usGfbaagUfbaacCfbaGfbaGfbaagcuasg	171	P-000039	UGUUAACCCCGGUUA	325	usgsuuaacCfcCfbaGfbaagcuagca	479	412
SRS-000040	G-000012	UUCUAGGCUUGGAACCGGGGUAA	18	usUfbaagGfbaagGfbaAfbaCfbaagcuasg	172	P-000040	ACCCCGGUUAACCCCGGUUA	326	asascgcGfbaUfuCfbaGfbaagcuagca	480	416
SRS-000041	G-000036	UCUCUAGGCUUGGAACCGGGGUAA	19	usCfbaagUfbaagGfbaAfbaCfbaagcuasg	173	P-000041	CCCGGUUAACCCCGGUUA	327	cscscggUfuCfbaAfbaGfbaagcuagca	481	417
SRS-000042	G-000037	UGCCUUCUAGGCUUGGAACCGGGG	20	usGfbaagUfbaagUfuGfbaAfbaGfbaagcuasg	174	P-000042	CCGGUUAACCCCGGUUA	328	csgsgmuacCfcAfbaGfbaagcuagca	482	419
SRS-000043	G-000013	UAGCCUUCUAGGCUUGGAACCGGGG	21	usAfbaagcuCfbaagCfbaUfuGfbaagcuasg	175	P-000043	CGGUUAACCCCGGUUA	329	csgsgmuacCfbaAfbaGfbaagcuagca	483	420

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transer
SRS-000044	G-000038	UGAGCCUUAAGCCUUGGAACCGG	22	usCfsgagccUfucugGfcUfuGfagaccsgsg	176	P-000044	GGUUCCAAAGCCUAGAGGCCUCA	330	gsgsuuccAfaGfcCfugagagcua	484	421
SRS-000045	G-000039	UGAAGGAGCCUUAAGCCUUGGAA	23	usCfsgaaggAfgccuCfuAfgGfucuggsasa	177	P-000045	CCAAGCCUAGAGGCCUCCUUA	331	cscsaagcCfuAfgAfgcuccuua	485	425
SRS-000046	G-000040	UCGGAAGGAGCCUUAAGCCUUGG	24	usCfsggaagGfagccCfuAfgGfucugsgsg	178	P-000046	AAGCCUAGAGGCCUCCUCCGA	332	asaagccuAfgAfgGfucuccga	486	427
SRS-000047	G-000041	UGUUCGGAAGGAGCCUUAAGCCU	25	usCfsguuegGfagagAfgCfcUfucaggsesu	179	P-000047	CCUAGAGGCCUCCUCCGAACA	333	cscsuagaGfgCfuCfucuccgaaca	487	430
SRS-000048	G-000042	UUGCUUGUUCGGAAGGAGCCUUCU	26	usUfsgcuuGfhuuegGfaAfgGfagccuscu	180	P-000048	AGGCUCCUCCGAACAAGCAA	334	asgsgcucCfuUfcCfgaacaagcaa	488	435
SRS-000049	G-000043	UGUGCUUGUUCGGAAGGAGCCUUC	27	usCfsguueuUfugucGfgAfaGfagccusuc	181	P-000049	GGCUCCUCCGAACAAGCACA	335	gsgscuccUfuCfcGfcaacaagcua	489	436
SRS-000050	G-000044	UCGGUUCUUGUUCGGAAGGAGCC	28	usCfsgguugCfugugUfucGfgAfgaggsesc	182	P-000050	CUCCUCCGAACAAGCACC	336	csusccuucCfcGfaAfcuagccaga	490	438
SRS-000051	G-000045	UUCGGUUGCUUGUUCGGAAGGAGC	29	usUfscggugGfucugUfucGfgGfagagsgsc	183	P-000051	UCCUCCGAACAAGCACC	337	uscsuucCfagAfaCfagaccagaa	491	439
SRS-000052	G-000046	UCAGUCGGUUGCUUGUUCGGAAGG	30	usCfsgagucGfugugUfuGfuUfuggaagsg	184	P-000052	UCCCGAACAAGCACCAGCUGA	338	ususcgaAfaAfaCfaccagacuga	492	442
SRS-000053	G-000047	UUGUCACUGCGUGUGUUGUUCGCG	31	usUfsguucAfgucugGfuGfcUfugucsgsg	185	P-000053	GAACAAGCACCAGCUGAGCAA	339	gsasacuaGfcAfcCfagucagcua	493	446
SRS-000054	G-000048	UUAGCACUUCUGCACCCACGCC	32	usUfsgagacCfucugGfaAfcCfagaggsesc	186	P-000054	CCUGGGUGCAGGAGUGCUUA	340	cscsuaggGfugGfaAfgagagucuaa	494	470
SRS-000055	G-000049	UGUAGCACUUCUGCACCCACGCC	33	usCfsguagcAfcuucUfugCfagCfaccagsgsc	187	P-000055	CUUGGGUGCAGGAGUGCUACA	341	csusggggUfugCfagCfagagucuaa	495	471
SRS-000056	G-000050	UGAUAAACUUCUGUCCAUUACCAUG	34	usCfsgauaaCfucugUfucCfauUfuaccasug	188	P-000056	UGGUAAUGGACAGAGUUAUCA	342	usgsguuaUfugGfagCfagaguuuaa	496	493
SRS-000057	G-000051	UCGAUAAACUUCUGUCCAUUACCAU	35	usCfsgauaaAfcuucGfuCfcAfuuaacsasu	189	P-000057	GGUAAUGGACAGAGUUAUCGA	343	gsgsuuaaUfugAfaAfgaguuuaega	497	494
SRS-000058	G-000052	UUAUUGUGCCUGGAUAACUCUGUC	36	usUfsgaugGfucucGfaUfaAfcuucggsuc	190	P-000058	CAGAGUUUUCGAGGCCACAUAA	344	csasagauUfaUfucGfagagcacaaua	498	503
SRS-000059	G-000053	UGUAUUGUGCCUGGAUAACUCUGU	37	usCfsguauugUfugucCfugAfuAfcuucgsu	191	P-000059	AGAGUUUUCGAGGCCACAUACA	345	asgsaguuAfuCfagAfggacauaca	499	504
SRS-000060	G-000054	UAGUAUUGUGCCUGGAUAACUCUG	38	usAfgsuauGfugccUfucGfaUfaucsuusg	192	P-000060	GAGUUUUCGAGGCCACAUACUA	346	gsasguuaUfucGfaCfagacaua	500	505
SRS-000061	G-000055	UACAGUGUGUGGAUUGUGCCUC	39	usAfgsuauGfugccUfucGfaUfagccuuc	193	P-000061	GGCACAUACUCCACCCACUGUA	347	gsgscacaUfaCfuCfaccacugua	501	515
SRS-000062	G-000056	UACCAAGCUUGGCAAGGUUCUCC	40	usAfgcaaaGfucugGfaAfgGfhuucsuusc	194	P-000062	AAGAAUCCGCCAACGCUUGGUA	348	asaagaacCfuGfcCfagcunggua	502	541
SRS-000063	G-000057	UAUGACCAAGCUUGGCAAGGUUCU	41	usAfgsuagCfagccUfuGfGfaggsuusc	195	P-000063	AACUUGCCAAAGCUUGGUAUA	349	asascugCfcaAfaGfucfugugcuaa	503	544
SRS-000064	G-000058	UAGAUAGACCAAGCUUGGCAAGGUU	42	usAfgsuagAfcuaaGfuUfuGfaggsusu	196	P-000064	CCUGCCAAAGCUUGGUAUAUA	350	cscsuagcAfaGfcUfugugcuaa	504	546
SRS-000065	G-000059	UUACCGUGGUAGCACUCCUUCAC	43	usUfscagcUfuguaGfaAfcUfucggsuusc	197	P-000065	GCAGGAGUGCUUACCGGUAUA	351	gscsaggaGfuGfcUfaccacgguaa	505	1162

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transer ipt
SRS-000066	G-000014	UUUACCGUGGUAAGCAGCUCCUGCA	44	usUfuaaccGfugguAfgCfAcfucucgacsa	198	P-000066	CAGGAGUGGUACCAACGGUAAA	352	csagggagUfgCfuAfcacagguaaa	506	1163
SRS-000067	G-000060	UCAUUACCGUGGUAAGCAGCUCCUG	45	usCfuaauaCfugguGfuAfgCfucucussug	199	P-000067	GGAGUGGUACCAACGGUAAUGA	353	gsgsagugCfuAfcCfagcguuauga	507	1165
SRS-000068	G-000061	UGUCCAUUACCGUGGUAAGCAGCUC	46	usCfuaucalUfuaccGfuGfugUfagcacsuc	200	P-000068	GUGCUACCAACGGUAAUGGACA	354	gsgugcuacCfcAfcCfuguaugagaca	508	1168
SRS-000069	G-000015	UUGUCCAUUACCGUGGUAAGCAGCU	47	usUfsguaccAfuaccCfugUfgGfuagcacsu	201	P-000069	UGCUACCAACGGUAAUGGACAA	355	usgscuacCfAfcCfugfuaugagaca	509	1169
SRS-000070	G-000062	UUCUGUCCAUUACCGUGGUAAGCAGC	48	usUfscugucCfcauuAfcCfugUfsguagcsc	202	P-000070	CUACCAACGGUAAUGGACAGAA	356	cusuaccacCfugGfuAfaugagacagaa	510	1171
SRS-000071	G-000016	UCUCUGUCCAUUACCGUGGUAAGCAGC	49	usCfscugucUfcauUfAfcCfcGfugucagac	203	P-000071	UACCAACGGUAAUGGACAGAGA	357	usaccacGfugUfaAfuGfagacagaga	511	1172
SRS-000072	G-000063	UAAUCUCUGUCCAUUACCGUGGUA	50	usAfuaccucUfguccAfuUfAfcCfuguggsua	204	P-000072	CCACGGUAAUGGACAGAGUUA	358	cscsacggUfaAfuGfagacagguua	512	1174
SRS-000073	G-000064	UGAUUACUCUGUCCAUUACCGUG	51	usCfuaauaCfucugUfcCfuUfuaccgusug	205	P-000073	CGGUAAUGGACAGAGUUAUCA	359	csgsguuaUfgGfuAfcCfagaguuaca	513	1177
SRS-000074	G-000065	UCGAUAAUCUCUGUCCAUUACCGU	52	usCfsguuaAfuucUfGfuAfcfuaccgsu	206	P-000074	GGUAAUGGACAGAGUUAUCGA	360	gsgsuuaaGfugAfcAfcaguuuacga	514	1178
SRS-000075	G-000066	UACAGGAUCUGGAUUCUGGAGU	53	usAfcicaggAfuucGfuUfAfcCfugcaggsu	207	P-000075	UGCAGGAUUCAGAGUCCUGUA	361	usgscaggAfuUfcCfagauccugua	515	2684
SRS-000076	G-000067	UAAUAAAGGGGUCGCCACAGGAGC	54	usAfuauaaGfgggcUfgCfcAfcaggsuac	208	P-000076	UCCUGUGGACGCCCUUAUUA	362	uscsugucGfugCfAfcCfcccuaauua	516	2698
SRS-000077	G-000068	UAAACAUAAAGGGGUCGCCACAGG	55	usAfuaccalUfaaggGfugCfuGfcccagsg	209	P-000077	UGUGGACAGCCCUUAUUGUUA	363	usgsgggcAfgCfcCfcuuuaugua	517	2701
SRS-000078	G-000069	UGUAUAAACAAUAAAGGGGUGGCCA	56	usCfuaauaAfcuaaAfuCfugGfugcscsa	210	P-000078	GCAGCCCUUAUUGUUAUACA	364	gscsagccCfcUfuAfuuguuuaaca	518	2705
SRS-000079	G-000070	UCGUUAAACAAUAAAGGGGUCGCC	57	usCfsguuaAfucaUfuAfgGfugcgscc	211	P-000079	CAGCCCUUAUUGUUAUACGA	365	csagggccCfuUfaUfuguuuaacga	519	2706
SRS-000080	G-000071	UUCGUUAAACAAUAAAGGGGUCG	58	usUfscguuAfuacaAfuAfuGfugcgsuc	212	P-000080	AGCCCUUAUUGUUAUACGAA	366	agsgccccUfuAfuUfuuuaucgaa	520	2707
SRS-000081	G-000072	UUGUGUCAGGUGGAGUACUCC	59	usUfsgugucCfagguUfgCfuGfuaccscsc	213	P-000081	GAGUACUUGCAACCUUGACACAA	367	gssaguuacUfgCfuAfcCfugcagaca	521	2747
SRS-000082	G-000017	UAUUGUGUCAGGUGGAGUACUAC	60	usAfuugugUfuaccGfuUfgCfagucacsuc	214	P-000082	GUACUGCAACCUUGACACAAUA	368	gssuaccacCfuAfcCfugacacaaua	522	2749
SRS-000083	G-000073	UGCAUUGUGUCAGGUGGAGUAC	61	usCfscuuuGfugucAfgGfuUfagcuaac	215	P-000083	ACUGCAACCUUGACACAAUGCA	369	ascsugcaAfcCfuGfagacaauca	523	2751
SRS-000084	G-000074	UGAGCAUUGUGUCAGGUGGAGU	62	usCfsgagcaUfugugUfcAfgGfugcaggsu	216	P-000084	UGCAACCUUGACACAAUGCUCA	370	usgscaacCfuGfuCfacaauuca	524	2753
SRS-000085	G-000075	UUGAGCAUUGUGUCAGGUGGAG	63	usUfsgagcaAfuugGfuUfAfgGfugcgsag	217	P-000085	GCAACCUUGACACAAUGUCUAA	371	gscsaaccUfgAfcAfcuaugcucaa	525	2754
SRS-000086	G-000018	UUGGUCUCUGAGCAUUGUGUCAGG	64	usUfsgcguCfugagCfuUfGfugucagsg	218	P-000086	UGACACAAUGCUCAGACGCAA	372	usgscacAfaUfGfucagagagaa	526	2760
SRS-000087	G-000076	UUCUGGUCUCUGAGCAUUGUGUCA	65	usUfscgcGfucugAfgCfuUfugucscsa	219	P-000087	ACACAAUGCUCAGACGCAAGAA	373	ascsacaalUfgCfuCfagcagcagaa	527	2762

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transcr ipt
SRS-000088	G-000077	UCUUUCGUCUGACGAUUGUU	66	usCfisuucGfegucUfgAfgCfauugusgu	220	P-000088	ACAAUGUCUACGACGCAAGA	374	asasaugCfuCfuCfagagagaaga	528	2764
SRS-000089	G-000078	UGAGCCUCUAGGCUUGGAAUCGG	67	usCfifagccUfueugGfuCfuGfauusgs	221	P-000089	GAUUCCAAAGCCUAGAGGCUCA	375	gasauuccAfuAfgCfueagagcuca	529	2815
SRS-000090	G-000079	UUUCAGAAAGGAGCCUCUAGGCUU	68	usUfaucaagAfiaggaGfcCfuCfiaggsusu	222	P-000090	GCCUAGAGGCUCCUUCUGAAA	376	gscsuagAfgGfcUfuccuugaaa	530	2823
SRS-000091	G-000080	UUUGCUCAGUUGGUGUUGUUCU	69	usUfauagcCfaguuGfgUfgCfueguusca	223	P-000091	AACAAAGCAACCAACUGAGCAAA	377	asasaagCfuCfuAfiuagagcaaa	531	2841
SRS-000092	G-000081	UCUUUGCUCAGUUGGUGUUGUUCU	70	usCfisuugCfueagUfuCfuGfgUfueguusuu	224	P-000092	CAAGCACCAACUGAGCAAGA	378	asasagcaCfuCfuCfugagcaaga	532	2843
SRS-000093	G-000082	UGUGCCUUGAUAAACUCUGUCCAU	71	usCfifagccUfueguAfuCfuCfueguusuu	225	P-000093	GGACAGAGUUAUCAAAGGCACA	379	ggsasacAfgUfuAfuacagacaca	533	2894
SRS-000094	G-000083	UGGAUCUGGUAUUCGGCAGUAGU	72	usCfifagccUfueguUfuCfuGfgUfueguusgu	226	P-000094	UACUGCCGAAAUCCAGAUCCA	380	uasacugcCfuAfuAfuacagaucca	534	3023
SRS-000095	G-000084	UUAAACACCAAGGGGCUGCCACAG	73	usUfisaacaCfueagGfgGfcUfuecaasag	227	P-000095	GUGGCAAGCCCUUGGUGUUA	381	gsusggcaGfcCfcCfuegguguuua	535	3044
SRS-000096	G-000085	UGUAUAAACACCAAGGGGCUGCCA	74	usCfifagccUfueguUfuCfuGfgUfueguusca	228	P-000096	GCAGCCCUUGGUGUUAUACA	382	gscsagccCfuCfuGfguguuuaaca	536	3047
SRS-000097	G-000086	UUUGUAUAAACACCAAGGGGCUGCCA	75	usUfisauguaUfuaacaCfuAfuGfegguusgc	229	P-000097	AGCCCUUGGUGUUAUACA	383	asgscccuUfuGfgUfueguuuuaaaa	537	3049
SRS-000098	G-000087	UGUUUGUAUAAACACCAAGGGGCUGCCA	76	usCfifagccUfueguUfuCfuGfgUfueguusgu	230	P-000098	GCCCUUGGUGUUAUACA	384	gscscccuUfgGfuGfuuuuuaaca	538	3050
SRS-000099	G-000088	UUCGUUGUACAGGUUGCAGUACUCC	77	usUfisaugUfueguUfuCfuGfgUfueguusgc	231	P-000099	AGUACUUGCAACCUUGACACGAA	385	asgsuacuGfcAfuCfuegagacgaa	539	3090
SRS-000100	G-000089	UAGCAUCGUUGUACAGGUUGCAGUA	78	usAfiagcaucCfueguCfuCfuGfgUfueguusua	232	P-000100	CUGCAACCUUGACACAGUUGCUA	386	csusgcaacCfuCfuAfuacagugua	540	3094
SRS-000101	G-000090	UGAGCAUCGUUGUACAGGUUGCAGU	79	usCfifagccUfueguUfuCfuGfgUfueguusgu	233	P-000101	UGCAACCUUGACACAGUUGCUA	387	uagcaaacCfuCfuGfgCfuegagcuca	541	3095
SRS-000102	G-000091	UUGAGCAUCGUUGUACAGGUUGCAGU	80	usUfisaugUfueguUfuCfuGfgUfueguusgc	234	P-000102	GCAACCUUGACACAGUUGCUA	388	gscsaaccUfgAfuAfuacagucuaa	542	3096
SRS-000103	G-000092	UUUGAGCAUCGUUGUACAGGUUGCAGU	81	usUfisaugUfueguUfuCfuGfgUfueguusgc	235	P-000103	AACCUUGACACAGUUGCUA	389	asasccugAfuAfuAfuacagucuaa	543	3098
SRS-000104	G-000093	UAAAGCCUUCUAGGCUUGGAGCCA	82	usAfiagcaucCfueguUfuCfuGfgUfueguusca	236	P-000104	GCUCCAAAGCCUAGAGGCUUUA	390	gscsuaccaAfgCfuCfuegagcuuaa	544	3158
SRS-000105	G-000094	UCCAUAAUUGGUAGUAGCAUUCU	83	usCfifagccUfueguUfuCfuGfgUfueguusca	237	P-000105	GACUGCUACUACCAUUAUGGA	391	gsasccugCfuCfuAfuacauuagga	545	3218
SRS-000106	G-000095	UUCCAUAAUUGGUAGUAGCAUUCU	84	usUfisaugUfueguUfuCfuGfgUfueguusgc	238	P-000106	ACUGCUACUACCAUUAUGGA	392	ascsugcuAfuCfuAfuacauuagga	546	3219
SRS-000107	G-000096	UGUCCAUAAUUGGUAGUAGCAUUCU	85	usCfifagccUfueguUfuCfuGfgUfueguusca	239	P-000107	CUGCUACUACCAUUAUGGA	393	csusggcuCfuAfuAfuacauuagga	547	3220
SRS-000108	G-000097	UUUCGUCCAUAAUUGGUAGUAGCA	86	usUfisaugUfueguUfuCfuGfgUfueguusca	240	P-000108	CUACUACCAUUAUGGACAGAA	394	csusacuaCfuAfuUfuegagacaga	548	3223
SRS-000109	G-000098	UAAUCUCUGUCCAUAAUUGGUAGUA	87	usAfiagcaucUfueguUfuCfuGfgUfueguusca	241	P-000109	CUACCAUUAUGGACAGAGUUA	395	csusaccaUfuAfuGfagagaguuua	549	3226

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transcr ipt
SRS-000110	G-000019	UUAAUCUCUGUCCAUAAUGGUAGU	88	usUfisaucUfugacCfaUfaAfuuguasgu	242	P-000110	UACCAUUAUGGACACAGAUUA	396	ussaccaUfaUfgGfaccagaguaa	550	3227
SRS-000111	G-000020	UCCAAAGCUUGGCAAGUUCUCCU	89	usCfisaagCfuugCfaAfgUfucuescu	243	P-000111	GAAAGAACTUUGCCAAAGCUUGGA	397	gsasagaaCfuUfgCfcaagcuugga	551	3276
SRS-000112	G-000021	UAGAUAGACCAAGCUGGCAAGU	90	usAfsaagAftcaagGfcUfuGfgcaagsu	244	P-000112	CUTUGCCAAAGCUTUGGUCAUCUA	398	csusugccAfaGfcUfugucaucua	552	3282
SRS-000113	G-000099	UAUAGAUAGACCAAGCUGGCAAG	91	usAfsaagaUfgaccAfaGfcUfugcasag	245	P-000113	UGCCAAAGCUTUGGUCAUCUAUA	399	usgsccaaGfcUfuGfgucaucuaa	553	3284
SRS-000114	G-000100	UCAUAGAUAGACCAAGCUTUGGCAA	92	usCfisaagAfuagacCfaAfgCfuugcsasa	246	P-000114	GCCAAAGCUTUGGUCAUCUAUGA	400	gsccaaagCfuUfgGfucuaucuaa	554	3285
SRS-000115	G-000101	UACUUAUCUGUGUGUGUGUCAUA	93	usAfsucauGfucggUfgUfgGfugucausa	247	P-000115	UGACACACACACAGCAUAAGUA	401	uugsacacCfaCfaCfcaagcaugua	555	3303
SRS-000116	G-000102	UGACUUAUCUGUGUGUGUGUCAU	94	usCfisaucUfugcuGfuGfuGfgucasa	248	P-000116	GACACCACACACAGCAUAAGUA	402	gsasaccAfaAfcCfagcaugua	556	3304
SRS-000117	G-000103	UCGACUUAUCUGUGUGUGUGUCA	95	usCfisaucUfugcuGfuGfuGfgucasa	249	P-000117	ACACCACACACAGCAUAAGUA	403	ascacacCfaCfaCfcaagcaugua	557	3305
SRS-000118	G-000104	UUCGACUUAUCUGUGUGUGUGUGU	96	usUfiscgaCfuagCfaGfgUfugugugau	250	P-000118	ACCACACACAGCAUAAGUGGAA	404	ascacacCfaAfgCfcaagucggaa	558	3307
SRS-000119	G-000105	UGUCCGACUUAUCUGUGUGUGUGUG	97	usCfisaucUfucuaGfcUfgGfugugugug	251	P-000119	CCACACACAGCAUAAGUGGACA	405	csacacacCfaGfcAfuagucggaca	559	3308
SRS-000120	G-000022	UGGUCCGACUUAUCUGUGUGUGUGU	98	usCfisaucUfucuaGfcUfgGfugugugug	252	P-000120	CACACCACAGCAUAAGUGGACCA	406	csasaccAfgCfaUfagucggacca	560	3309
SRS-000121	G-000106	UUUUUCUGGGGUCGACUUAUCUG	99	usUfisaucUfugcuGfcCfaCfuagucsu	253	P-000121	GCAUAGUCGGGACCCACAGAAAA	407	gscauagUfcaGfgAfcaccagaaaa	561	3316
SRS-000122	G-000107	UUUUUCUGGGGUCGACUUAUCUG	100	usUfisaucUfugcuGfcCfaCfuagucsu	254	P-000122	CAUAGUCGGGACCCACAGAAAA	408	csasuaguUfcaGfgAfcaccagaaaa	562	3317
SRS-000123	G-000108	UUAGUUUUUCUGGGGUCGACUUAU	101	usUfisaucUfugcuGfcCfaCfuagucsu	255	P-000123	AGUCGGGACCCACAGAAAACUAA	409	agsuagcAfaCfcCfagaaacuaa	563	3320
SRS-000124	G-000109	UAUCCAUUGUGUUAACACCAAGG	102	usAfsucaUfugcuGfuAfaAfcacagsg	256	P-000124	CUUGGUUUACACCAUUGGUAUA	410	csusugcuGfuUfaCfaccagugua	564	3396
SRS-000125	G-000110	UGAUUCCAUUGUGUUAACACCAAG	103	usCfisaucUfugcuGfuAfaAfcacagsg	257	P-000125	UUUGGUUUACACCAUUGGUAUA	411	usugugUfcaAfaAfcacagugua	565	3397
SRS-000126	G-000111	UGGAUCCAUUGUGUUAACACCAAG	104	usCfisaucUfugcuGfuAfaAfcacagsg	258	P-000126	UGGUUUUUACACCAUUGGUAUA	412	usugugUfcaCfaCfcaagugua	566	3398
SRS-000127	G-000112	UGGAUCCAUUGUGUUAACACCAAG	105	usCfisaucUfugcuGfuAfaAfcacagsg	259	P-000127	GGUUGUUUUACACCAUUGGUAUA	413	gsguguuAfaAfaCfcaagugua	567	3399
SRS-000128	G-000113	UTGACACUUGGUAUCCACCAAGG	106	usUfisaucUfugcuGfuAfaAfcacagsg	260	P-000128	CACCAUUGGUAUCCACCAAGGUA	414	csasccauGfgAfaCfcaagugua	568	3406
SRS-000129	G-000114	UCUACACUUGGUAUCCACCAAGG	107	usCfisaucUfugcuGfuAfaAfcacagsg	261	P-000129	ACCAUUGGUAUCCACCAAGGUA	415	ascacauGfaUfcaCfcaagugua	569	3407
SRS-000130	G-000115	UGUUUCAAAGGACACUUGAUUCUG	108	usCfisaucUfugcuGfuAfaAfcacagsg	262	P-000130	GAAUCAAAGGACUUGGUAUCC	416	gsasaucaAfgUfcaCfcaagugua	570	3464
SRS-000131	G-000116	UCAUGGUUAUAAACACCAAGGACUA	109	usCfisaucUfugcuGfuAfaAfcacagsg	263	P-000131	GUCCUUUGGUUAUAAACCAAGG	417	gsusccuuGfgUfcaCfcaagugua	571	3735

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transcr ipt
SRS-000132	G-000117	UUCCAUGGUUAACACCAAGGAC	110	usUfscacUfGfuaAfcaCfcaCfcaagsgasc	264	P-000132	CCUUGGUGUUUACCAUGGAA	418	cscsuuggUfGfuaAfuaaccauggaa	572	3737
SRS-000133	G-000118	UAUCCAUGGUUAACACCAAGGA	111	usAfaucaUfGfuaUfcaAfcaCfcaagsgsa	265	P-000133	CUUGGUGUUUACCAUGGUA	419	csusugguGfuaUfcaUfaccuaggaua	573	3738
SRS-000134	G-000119	UGGAUCCAUUGGUUAACACCAA	112	usGfsggaUfcaagGfuaAfuaAfcaaccsasa	266	P-000134	GGUGUUUAACCAUGGAUCCCA	420	gsgsuguuAfuaAfcaCfcauggauccca	574	3741
SRS-000135	G-000120	UGACAUUGUGUCAGGUGUAGUA	113	usGfscacuUfGfuaUfcaCfcaGfGfugcagsusa	267	P-000135	CUGCAACCCUGACACAAUGUCA	421	csusgcaaCfcaUfGfAfcaacauguca	575	3778
SRS-000136	G-000121	UGGACAUUGUGUCAGGUUGCAGU	114	usGfsgacaUfGfuaUfcaAfGfGfuaagcagsu	268	P-000136	UGCAACCCUGACACAAUGUCA	422	ugsacaacCfcaUfcaCfcaacaugucca	576	3779
SRS-000137	G-000122	UUGGACAUUGUGUCAGGUUGCAG	115	usUfsggacAfuaagGfuaCfcaGfGfuaagcagsu	269	P-000137	GCAACCCUGACACAAUGUCCAA	423	gscsaaccUfGfAfcaAfcaauguccaa	577	3780
SRS-000138	G-000123	UCACUGGACAUUGUGUCAGGUUG	116	usCfscacugGfcaacuUfGfUfGfUfcaaggsusg	270	P-000138	ACCUGACACAAUGUCCAGUGA	424	ascscuugaCfcaCfcaAfuauguccaguga	578	3783
SRS-000139	G-000124	UAUUCUGUCACUGGACAUUUGUGU	117	usAfauacuGfhuacUfGfGfcaCfcaugusgsu	271	P-000139	ACAUGUCCAGUGACAGAAUA	425	ascsaauGfcaCfcaGfcaGfugacagaua	579	3790
SRS-000140	G-000125	UCACCAUUGGGUAGUAUUCUGU	118	usCfscacuUfhuaggGfuaAfGfUfauucsgsu	272	P-000140	AGAUAUACUACCCAAUUGGUGA	426	agsgaauCfcaAfcaCfcaaauggguga	580	3991
SRS-000141	G-000126	UGUAUAACACCAAGGCGAAUUCU	119	usGfhuuaAfcaacAfcaGfGfGfcauacscu	273	P-000141	AUUCGCCUUGGUGUUUAUACA	427	asusucgcCfcaUfcaGfGfuguuuaaca	581	4049
SRS-000142	G-000127	UCAUGGUUAACACCAAGGCGA	120	usCfhuaggUfauuaCfcaCfcaAfcaaggcgsa	274	P-000142	GCCUUGGUGUUUAUACCAUGA	428	gscscuucGfGfUfGfUfuaaccauga	582	4053
SRS-000143	G-000128	UUCCAUGGUUAACACCAAGGOC	121	usUfscacuGfhuuaAfcaCfcaCfcaagsgsc	275	P-000143	CCUUGGUGUUUAUACCAUGGAA	429	cscsuuggUfGfUfuaAfuaaccauggaa	583	4055
SRS-000144	G-000129	UAUCCAUGGUUAACACCAAGGG	122	usAfaucaUfGfuaUfcaAfcaagsgsg	276	P-000144	CUUGGUGUUUAUACCAUGGUA	430	csusugguGfuaUfcaUfaccuaggaua	584	4056
SRS-000145	G-000130	UUGACACUGGGAUCCAUUGGUUA	123	usUfsgacaCfhuaggAfhuCfcafuguausa	277	P-000145	UACCAUGGAUCCCAUGGUCAA	431	uasaccuGfGfAfhuCfcaugugucaa	585	4066
SRS-000146	G-000131	UCUGACACUGGGAUCCAUUGGUUA	124	usCfhuagAcfhuaggGfuaUfcaCfcaugusasu	278	P-000146	ACCAUGGAUCCCAUGGUCAA	432	ascscuagGfcaUfcaCfcaugugucaga	586	4067
SRS-000147	G-000132	UGGACACCCUGGGAUCCAUUGGAG	125	usGfsgaccAfccguGfGfGfcaGfhuugusagsg	279	P-000147	CACAACUCCCAUGGUUCCCA	433	csasacaUfcaCfcaAfcaaggugucca	587	4138
SRS-000148	G-000133	UGGGACACCCUGGGAUCCAUUGGA	126	usGfsggacCfaccgUfGfGfAfcaagsgsa	280	P-000148	ACAACUCCCAUGGUUCCAA	434	ascsaacuCfcaCfcaCfcaaggugucca	588	4139
SRS-000149	G-000134	UUGCUUGGAACUUGGACACCCGU	127	usUfsgcuuGfhuacUfGfGfAfcaaccgsu	281	P-000149	GGUGGUCCCAUGGUUCCAA	435	gsgsugguCfcaCfcaCfcauuccaagcaa	589	4150
SRS-000150	G-000135	UAUUCUGUCACUGGACAUUCGUU	128	usAfauacuGfhuacUfGfGfcaCfcaugusgsu	282	P-000150	ACGAUGUCCCAUGGACAAUA	436	ascsgaugUfcaCfcaCfcaGfugacagaua	590	4450
SRS-000151	G-000136	UGAUGCCAGUGUGGUUAUCAUAGA	129	usGfhuagCfhuaggUfGfGfAfcauuaagsga	283	P-000151	UAUGAUCCCAUGGACAAUA	437	uasugauAfcaCfcaCfcaugucca	591	4645
SRS-000152	G-000137	UUGAUGCCAGUGUGGUUAUCAUAG	130	usUfsgaugCfcaagGfuaGfGfUfauucuasag	284	P-000152	AUGAUACCAUGGCAUCAA	438	asusgaucCfcaAfcaAfcaugucca	592	4646
SRS-000153	G-000138	UGUGUAACACCAAGGUGUUTUCC	131	usGfhuuaAfcaacAfGfGfUfhuuuuscsc	285	P-000153	AAACAACCCUGGUGUACACA	439	asasacaCfcaCfcaGfGfuguaacaca	593	4733

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transcr ipt
SRS-000154	G-000139	UAGGACACCUAGAUUCUGUUCUG	132	usAfsagacAfecugAfuAfcUfguuucusug	286	P-000154	GAAACAGAAUACAGGUUCCUA	gsasacaGfaAfuAfcagguucua	440	4802
SRS-000155	G-000140	UUAGGACACCUAGAUUCUGUUCU	133	usUfsaggaCfaccuGfaUfuCfuguuususu	287	P-000155	AAACAGAAUACAGGUUCCUA	asasacagAfaUfaAfcgugucuaa	441	4803
SRS-000156	G-000141	UUCUAGGACACCUAGAUUCUGUTU	134	usUfsucagGfaccuGfaUfuCfuguuususu	288	P-000156	ACAGAAUACAGGUUCCUAGAA	ascsagaaUfaAfcGfugucuaagaa	442	4805
SRS-000157	G-000142	UCUCUAGGACACCUAGAUUCUGUTU	135	usCfsucuaGfagaaCfcUfgAfuucugsusu	289	P-000157	CAGAAUACAGGUUCCUAGAGA	csasgaauCfaGfgUfguccuagaga	443	4806
SRS-000158	G-000143	UGUCUUAAGGACACCUAGAUUCUG	136	usCfsucucUfaggaCfaCfcUfgauucusug	290	P-000158	GAAUACAGGUUCCUAGAGACA	gsasaucaGfgUfgUfrcuagagaca	444	4808
SRS-000159	G-000144	UGGAGUCUCUAGGACACCUAGAU	137	usCfsgagagUfucucAfgCfrcCfaccugasa	291	P-000159	CAGGUUCCUAGAGACUCCCA	csasggugUfrcCfuAfcgacucucca	445	4812
SRS-000160	G-000145	UGGAAACAACAGUGGAGUCUCUA	138	usCfsgaacAfacagUfgGfgAfgucucusa	292	P-000160	GAGACUCCACUUGUUGUCCA	gsasgacuCfrcCfrcCfuguuuucca	446	4823
SRS-000161	G-000146	UGAAUUGUCCUCUGAUACUCUGG	139	usCfssaagUfgccuCfrcAfuAfacucussg	293	P-000161	AGAGUUAUCGAGGCGACAUAUA	asgsaguuAfuCfrcAfcgacauuca	447	4926
SRS-000162	G-000147	UUGGAUGACCAAGAUUGACAUUG	140	usUfsggaugUfgccuAfgAfuUfgcausgsu	294	P-000162	AUGUCAAUUUGGUCAUCCAA	asusgucuaAfuCfuUfguucacaa	448	4969
SRS-000163	G-000148	UAUGGAUGACCAAGAUUGACAUUG	141	usAfsuggaUfgaccAfaGfaUfugacuasug	295	P-000163	UGUCAAUUUGGUCAUCCAU	usgsucaaUfrcUfuGfgucuaucua	449	4970
SRS-000164	G-000149	UAAAAACAAGGCGCUGUAUCG	142	usAfsaacAfcacCfrcCfrcCfuguuusug	296	P-000164	AUACAGGCCUUGGUUUUA	asasacagCfrcCfrcUfguguuuuu	450	5073
SRS-000165	G-000150	UGCAUUCGCGUCAGGUUGCAGUAC	143	usCfscacugGfsgucAfgGfuUfgcausasc	297	P-000165	ACUGCAACCTUGACGCGAUCCA	ascsuagcaAfcCfuGfagcggaugca	451	5121
SRS-000166	G-000151	UAGCAUCGCGUCAGGUUGCAGUA	144	usAfsagcauUfgccuAfgCfrcUfgcagsusa	298	P-000166	CUGCAACCTUGACGCGAUCCA	csusgcaacCfrcUfgAfcgcaugcua	452	5122
SRS-000167	G-000152	UGAGCAUCGCGUCAGGUUGCAGU	145	usCfsgagcaUfegagUfaAfgGfugcagsu	299	P-000167	UGCAACCTUGACGCGAUCCA	usgscaacCfuGfaCfrcggaugcua	453	5123
SRS-000168	G-000153	UUGAGCAUCGCGUCAGGUUGCAG	146	usUfsgagcaAfuagcGfuGfaGfugucgasa	300	P-000168	GCAACCTUGACGCGAUCCA	gscaaacUfgAfcGfrcggaugcua	454	5124
SRS-000169	G-000154	UUCUGAGCAUCGCGUCAGGUUGC	147	usUfscugagGfaucGfrcGfuCfaguuusug	301	P-000169	AACCTUGACGCGAUCCA	asascuagAfcGfrcGfagucagaa	455	5126
SRS-000170	G-000155	UGUCUAGAGCAUCGCGUCAGGUUG	148	usCfscugagUfgcauUfgCfrcUfgcagsusu	302	P-000170	ACCTUGACGCGAUCCA	ascscuagCfrcCfrcAfuugcagaca	456	5127
SRS-000171	G-000156	UUGUCUGAGCAUCGCGUCAGGUUG	149	usUfsgucucUfgagcaUfrcGfrcGfucagsusu	303	P-000171	CCUGACGCGAUCCA	csusgacGfrcCfrcAfuUfgucagaca	457	5128
SRS-000172	G-000157	UGUCUCUGAGCAUCGCGUCAGGUUG	150	usCfsgucucUfgagcaUfrcGfrcGfucagsusu	304	P-000172	CUGACGCGAUCCA	csusgacGfrcCfrcAfuUfgucagaca	458	5129
SRS-000173	G-000158	UUGUCUCUGAGCAUCGCGUCAGGUUG	151	usUfsgucucUfgagcaUfrcGfrcGfucagsusu	305	P-000173	UGACGCGAUCCA	usgsaacGfrcUfgCfrcuagacaca	459	5130
SRS-000174	G-000159	UUCUCUCUCUGAGCAUCGCGUCAG	152	usUfscugagUfgcauUfgCfrcUfgcagsusu	306	P-000174	ACGCGAUCCA	ascsgcagUfgCfrcCfrcuagacaca	460	5132
SRS-000175	G-000160	UUAACAUGUCUCCAGGACAUUUC	153	usUfsacaaUfgcuaCfrcAfgGfucuuusuc	307	P-000175	AAUGUCCUGGAAGCAUUGUA	asasugucCfuGfgAfcgcauugaa	461	5505

Compd ID	siRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO.	Modified Antisense Sequence (5'→3')	SEQ ID NO.	siRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO.	Modified Sense Sequence (5'→3')	SEQ ID NO.	Position at Human Transcr ipt
SRS-000176	G-000161	UCAGUGAUGUAACAUCAGUCCU	154	usCfsgugA fguuaA fcaAfuU fcaucscsu	308	P-000176	GACUGAAUGUUACAUCACUGA	462	gsascugaAfuGfuU fcaucacuga	616	5866
As used herein, "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "A" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytosine-3'-phosphate; "c" refers to 2'-O-methylcytosine-3'-phosphate; "C" refers to 2'-fluorocytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "G" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "U" refers to 2'-fluorouridine-3'-phosphate; "T" refers to thymine-3'-phosphate; "t" refers to 2'-O-methylthymine-3'-phosphate; "T" refers to 2'-fluorothymine-3'-phosphate; "I" refers to inosine-3'-phosphate; "i" refers to 2'-O-methylinosine-3'-phosphate; "I" refers to 2'-fluorinosine-3'-phosphate; "X" refers to xanthosine-3'-phosphate; "x" refers to 2'-O-methylxanthosine-3'-phosphate; "X" refers to 2'-fluoroxanthosine-3'-phosphate; "Y" refers to yridine-3'-phosphate; "y" refers to 2'-O-methylpyridine-3'-phosphate; "Y" refers to 2'-fluoropyridine-3'-phosphate; "N" refers to nucleoside-3'-phosphate; "n" refers to 2'-O-methylnucleoside-3'-phosphate; "N" refers to 2'-fluoronucleoside-3'-phosphate; "P" refers to phosphorothioate; "p" refers to 3'-phosphorothioate. The "position at human transcript" is defined as the 5' position of a 21-mer target site in human transcript (NCBI Reference Sequence No: NM_005577.4). Note that, in some instances, the sense strand sequence is coupled to a targeting moiety (e.g., GalNAc or galactose (e.g., L96)) at the 3' end of the sense strand.											

Conjugation

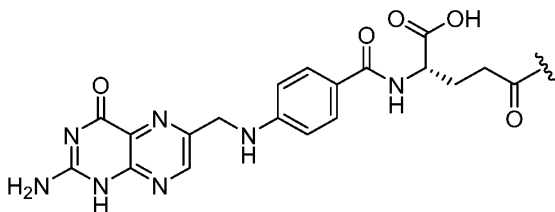
Targeting Moiety

[0158] In certain aspects, the polynucleotide molecule described herein is coupled or conjugated with one or more targeting moieties to form a polynucleotide-targeting moiety conjugate molecule. In some instances, a targeting moiety is selected based on its ability to target the conjugate molecule described herein to a desired cell population, tissue, or an organ selectively or preferably. In some instances, the targeting moiety targets the cell, tissue, or an organ that expresses the corresponding binding partner (e.g., either the corresponding receptor or ligand) of the targeting moiety. For example, the polynucleotide molecule described herein could be targeted to hepatocytes expressing asialoglycoprotein (ASGP-R) by selecting a targeting moiety containing N-acetyl galactosamine (GalNAc) as the targeting moiety. Any suitable GalNAc molecules that are known in the art to be used as a targeting moiety are contemplated. Exemplary GalNAc molecule includes a triantennary GalNAc (e.g., L96). A further example of the targeting moiety is galactose. The targeting moiety can also be a lipid, peptide, or small molecule.

[0159] A targeting moiety (i.e., an intracellular targeting moiety) that targets a desired site within the cell (e.g., endoplasmic reticulum, Golgi apparatus, nucleus, or mitochondria) may be included in the hybridized polynucleotide constructs disclosed herein. Non-limiting examples of the intracellular targeting moieties are provided in WO 2015/069932 and in WO 2015/188197; the disclosure of the intracellular targeting moieties in WO 2015/069932 and in WO 2015/188197 is incorporated herein by reference.

[0160] The polynucleotide molecule described herein, thus, may include one or more targeting moieties selected from the group consisting of intracellular targeting moieties, extracellular targeting moieties, and combinations thereof. Thus, the inclusion of one or more targeting moieties (e.g., extracellular targeting moieties including targeting moieties independently selected from the group consisting of folate, mannose, N-acetyl galactosamine, and prostate specific membrane antigen) and one or more intracellular targeting moiety (e.g., a moiety targeting endoplasmic reticulum, Golgi apparatus, nucleus, or mitochondria) in the polynucleotide molecule described herein can facilitate the delivery of the polynucleotides to a specific site within the specific cell population. In some aspects, the targeting moiety contains one or more mannose carbohydrates. Mannose targets the mannose receptor, which is a 175 KDa membrane-associated receptor that is expressed on sinusoidal liver cells and antigen presenting cells (e.g., macrophages and dendritic cells). It is a highly effective endocytotic/recycling receptor that binds and internalizes mannosylated pathogens and proteins (Lennartz et. al. J. Biol. Chem. 262:9942-9944,1987; Taylor et. al. J. Biol. Chem. 265:12156-62, 1990).

[0161] Some of the targeting moieties are described herein. In some aspects, the targeting moiety contains or specifically binds to a protein selected from the group including insulin, insulin-like growth factor receptor 1 (IGF1R), IGF2R, insulin-like growth factor (IGF; e.g., IGF 1 or 2), mesenchymal epithelial transition factor receptor (c-met; also known as hepatocyte growth factor receptor (HGFR)), hepatocyte growth factor (HGF), epidermal growth factor receptor (EGFR), epidermal growth factor (EGF), heregulin, fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), platelet-derived growth factor (PDGF), vascular endothelial growth factor receptor (VEGFR), vascular endothelial growth factor (VEGF), tumor necrosis factor receptor (TNFR), tumor necrosis factor alpha (TNF- α), TNF- β , folate receptor (FOLR), folate, transferrin, transferrin receptor (TfR), mesothelin, Fc receptor, c-kit receptor, c-kit, an integrin (e.g., an $\alpha 4$ integrin or a β -1 integrin), P-selectin, sphingosine-1-phosphate receptor-1 (S1PR), hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD4, CD11, CD18, CD20, CD25, CD27, CD52, CD70, CD80, CD85, CD95 (Fas receptor), CD106 (vascular cell adhesion molecule 1 (VCAM1), CD166 (activated leukocyte cell adhesion molecule (ALCAM)), CD178 (Fas ligand), CD253 (TNF-related apoptosis-inducing ligand (TRAIL)), ICOS ligand, CCR2, CXCR3, CCR5, CXCL12 (stromal cell-derived factor 1 (SDF-1)), interleukin 1 (IL-1), IL-1ra, IL-2, IL-3, IL-4, IL-6, IL-7, IL-8, CTLA-4, MART-1, gp100, MAGE-1, ephrin (Eph) receptor, mucosal addressin cell adhesion molecule 1 (MAdCAM-1), carcinoembryonic antigen (CEA), LewisY, MUC-1, epithelial cell adhesion molecule (EpCAM), cancer antigen 125 (CA125), prostate specific membrane antigen (PSMA), TAG-72 antigen, and fragments thereof. In further aspects, the targeting moiety contains erythroblastic leukemia viral oncogene homolog (ErbB) receptor (e.g., ErbB1 receptor; ErbB2 receptor; ErbB3 receptor; and ErbB4 receptor). In some aspects, the targeting moiety contains one or more (e.g., from 1 to 6) N-acetyl galactosamines (GalNAc). In some aspects, the targeting moiety contains one or more (e.g., from 1 to 6) galactose. In certain aspects, the targeting moiety contains one or more (e.g., from 1 to 6) mannoses. In other aspects, the targeting moiety contains a folate ligand. The folate ligand has the structure:



Certain targeting moieties may include bombesin, gastrin, gastrin-releasing peptide, tumor growth factors (TGF) (e.g., TGF- α or TGF- β), or vaccinia virus growth factor (VVGF). Non-peptidyl targeting moieties can also be used in the targeting moieties and may include, for example,

steroids, carbohydrates, vitamins, and lectins. Some targeting moieties may include a polypeptide, such as somatostatin or somatostatin analog (e.g., octreotide or lanreotide), bombesin, or an antibody or antigen-binding fragment thereof. Antibodies may be of any recognized class or subclass, e.g., IgG, IgA, IgM, IgD, or IgE. Typical are those antibodies which fall within the IgG class. The antibodies can be derived from any species according to techniques known in the art. Typically, however, the antibody is of human, murine, or rabbit origin. In addition, the antibody may be polyclonal or monoclonal, but is typically monoclonal. Human or chimeric (e.g., humanized) antibodies may be used in targeting moieties. Targeting moieties may include an antigen-binding fragment of an antibody. Such antibody fragments may include, for example, the Fab', F(ab')₂, Fv, or Fab fragments, single domain antibody, ScFv, or other antigen-binding fragments. Fc fragments may also be employed in targeting moieties. Such antibody fragments can be prepared, for example, by proteolytic enzyme digestion, for example, by pepsin or papain digestion, reductive alkylation, or recombinant techniques. The materials and methods for preparing antibody fragments are well-known to those skilled in the art. See, e.g., Parham, J. Immunology, 131:2895, 1983; Lamoyi et al., J. Immunological Methods, 56:235, 1983.

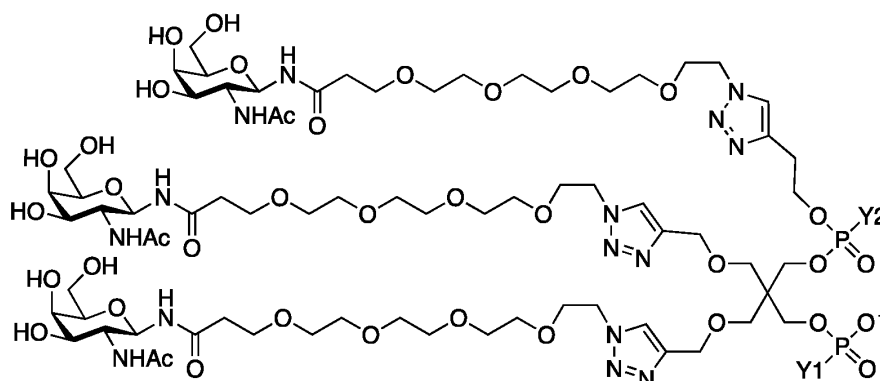
[0162] Other peptides for use as a targeting auxiliary moiety in polynucleotide molecule described herein can be selected from KiSS peptides and analogs, urotensin II peptides and analogs, GnRH I and II peptides and analogs, depreotide, vapreotide, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), RGD-containing peptides, melanocyte-stimulating hormone (MSH) peptide, neurotensin, calcitonin, glutathione, YIGSR (leukocyte-avid peptides, e.g., P483H, which contains the heparin-binding region of platelet factor-4 (PF-4) and a lysine-rich sequence), atrial natriuretic peptide (ANP), β -amyloid peptides, delta-opioid antagonists (such as ITIPP(ψ)), annexin-V, endothelin, leukotriene B₄ (LTB₄), chemotactic peptides (e.g., N-formyl-methionyl-leucyl-phenylalanine-lysine (fMLFK), GP IIb/IIIa receptor antagonists (e.g., DMP444), human neutrophil elastase inhibitor (EPI-HNE-2 and EPI-HNE-4), plasmin inhibitor, antimicrobial peptides, apticide (P280 and P274), thrombospondin receptor (including analogs such as TP-1300), bitistatin, pituitary adenyl cyclase type I receptor (PAC1), fibrin α -chain, peptides derived from phage display libraries, and conservative substitutions thereof.

[0163] One or more (e.g., from 1 to 6) targeting moieties can be linked to MOIETY or to X₂ in formula (V', V'', V''', V''', V''', V''') through –LinkA–.

[0164] In some aspects, the targeting moiety includes one or more (e.g., from 1 to 6 or from 1 to 3) asialoglycoprotein receptor ligands (e.g., GalNAc). In some aspects, an asialoglycoprotein receptor ligand (e.g., GalNAc) is attached to –LinkA– through an anomeric carbon (e.g., where the anomeric carbon is the carbon atom in an acetal or a hemiaminal). An asialoglycoprotein receptor ligand

(e.g., GalNAc) attached to a linker through a hemiaminal may produce a hybridized polynucleotide construct having superior efficacy in gene silencing as compared to hybridized polynucleotide constructs having the asialoglycoprotein receptor ligand (e.g., GalNAc) attached to a linker through an acetal.

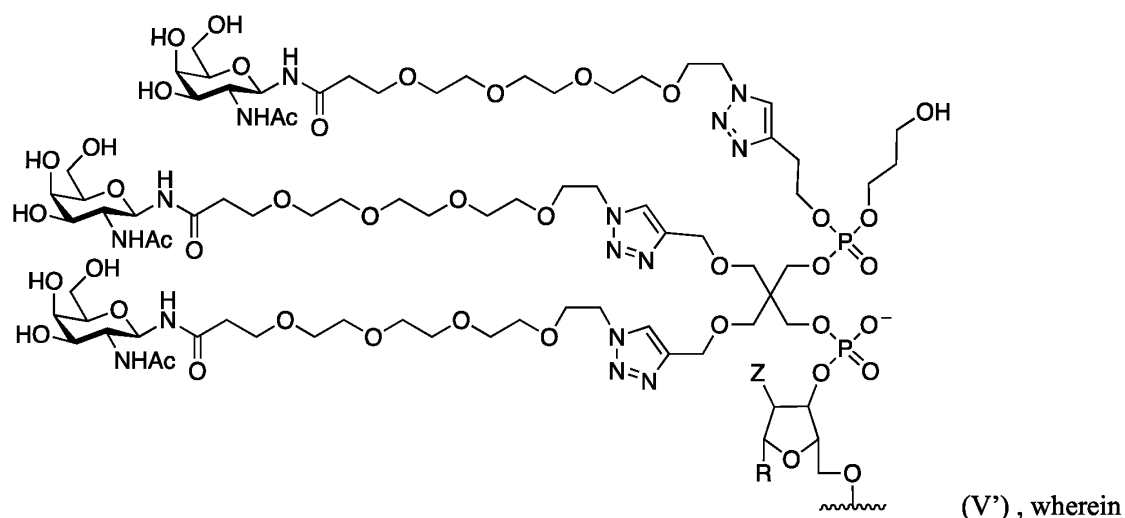
[0165] In some aspects, the linker and three asialoglycoprotein receptor targeting moieties, each of which comprises GalNAc, are as shown in Formula (V). In some instances, the conjugate described herein only comprises one asialoglycoprotein receptor targeting moiety, so the conjugate comprises a structure of Formula (V) with any two of the targeting moieties removed. In some instances, the conjugate described herein only comprises two asialoglycoprotein receptor targeting moieties, so the conjugate described herein comprises a structure of Formula (V) with any one of the targeting moieties removed.



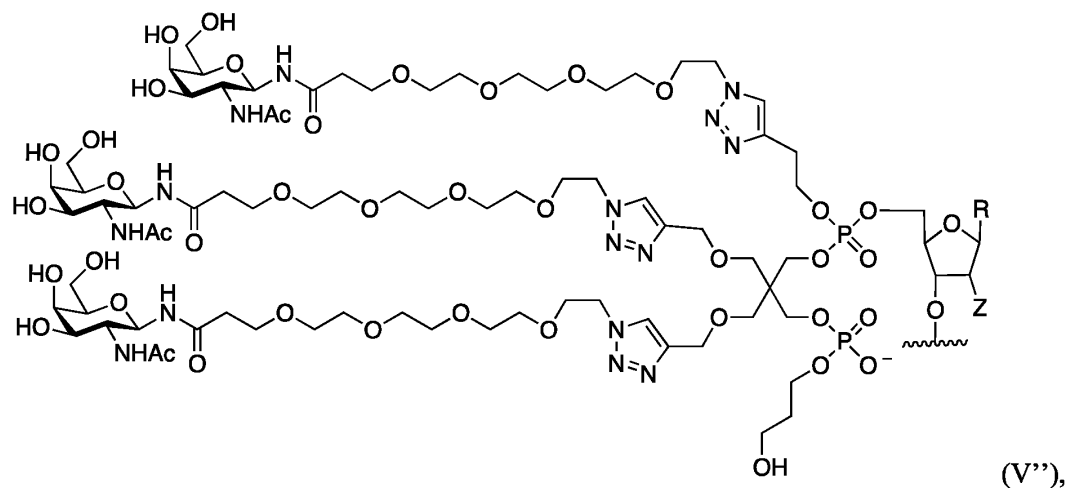
(V),

wherein one of Y1 and Y2 is nucleotide, or wherein both Y1 and Y2 are nucleotides and Y1 and Y2 are consecutive or neighboring nucleotides from the polynucleic acid molecule described herein.

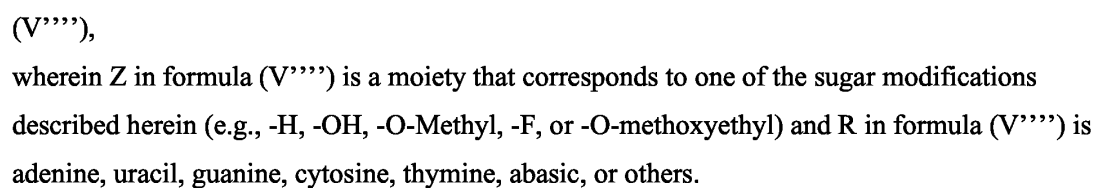
[0166] In some aspects, the linker and the targeting moieties described herein are conjugated to 3' end of the sense strand (e.g., as shown in Formula (V', V''', V''', V''')). In some aspects, the linker and the targeting moieties described herein are conjugated to 5' end of the sense strand (e.g., as shown in Formula (V'') or (V''')). In some aspects, the linker and the targeting moieties described herein are conjugated to 3' end of the antisense strand (e.g., as shown in Formula (V'), (V'''), (V'''), (V''')). In some aspects, the linker and the targeting moieties described herein are conjugated to 5' end of the antisense strand (e.g., as shown in Formula (V'') or (V''')).

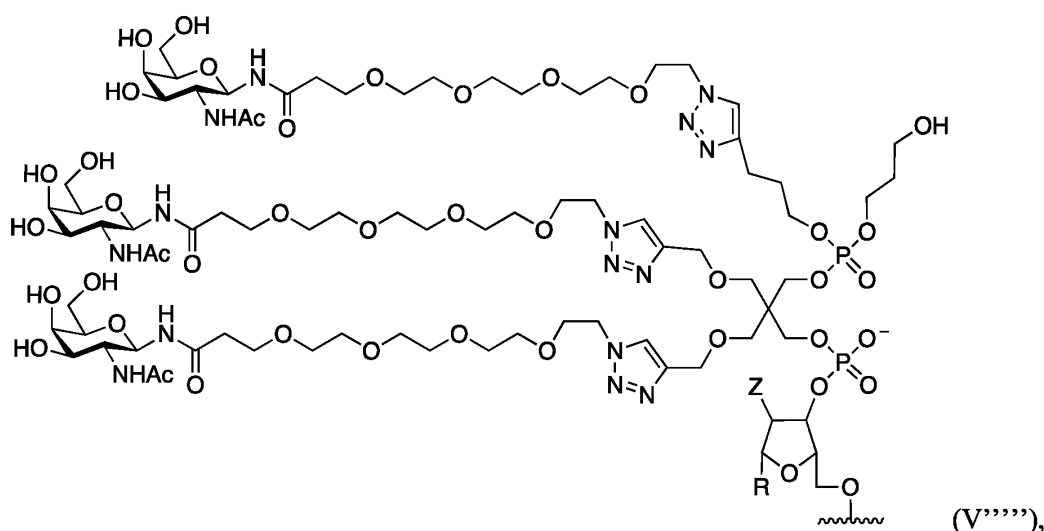


Z in formula (V') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others;

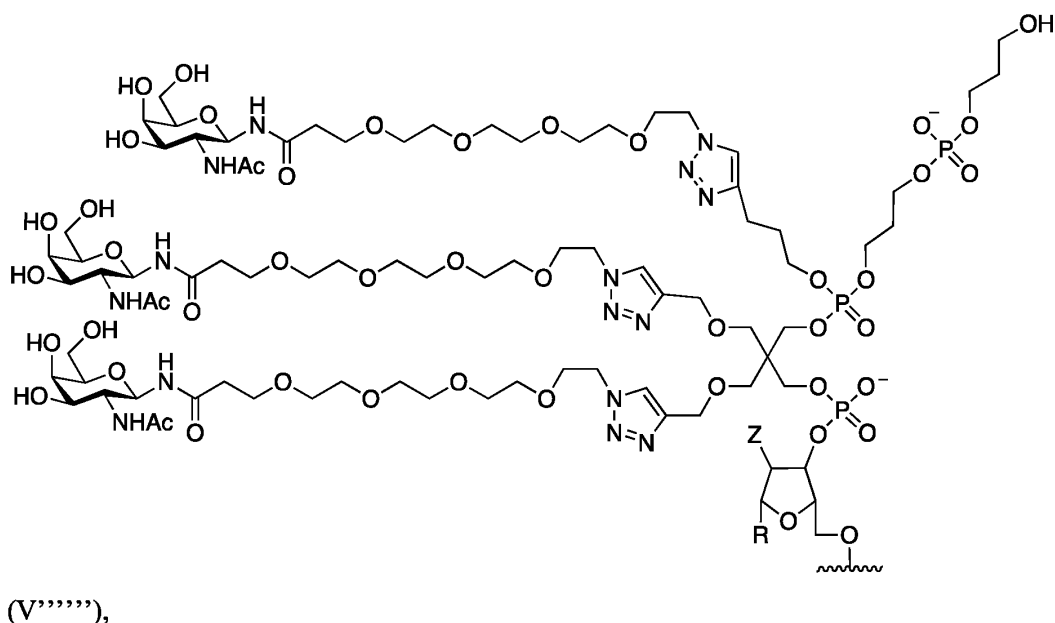


wherein Z in formula (V'') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V'') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[illegible]



wherein Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



wherein Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0167] In some instances, the 3' end of passenger/sense strand from Table 1, Table 2, or Table 5 is conjugated with X2-GalNAc (*see* Formula (V), (V'), (V'''), (V'''''), (V''''')). In some instances, the 5' end of passenger/sense strand from Table 1, Table 2, or Table 5 is conjugated with X2-GalNAc (*see* Formula (V), (V''), or (V''')). In some instances, a nucleic acid within

passenger/sense strand (not at the 5' or 3' end) from Table 1, Table 2, or Table 5 is conjugated with X2-GalNAc (*see* Formula (V)). In some instances, the 3' end of guide/antisense strand from Table 1, Table 2, or Table 5 is conjugated with X2-GalNAc (*see* Formula (V), (V'), (V'''), (V''''), (V''''')). In some instances, the 5' end of guide/antisense strand from Table 1, Table 2, or Table 5 is conjugated with X2-GalNAc (*see* Formula (V), (V''), or (V''')). In some instances, a nucleic acid within guide/antisense strand (not at the 5' or 3' end) from Table 1, Table 2, or Table 5 is conjugated with X2-GalNAc (*see* Formula (V)).

[0168] In some instances, one or more endosomal escape moieties (e.g., from 1 to 6 or from 1 to 3) can be attached to a polynucleotide construct or a hybridized polynucleotide construct disclosed herein as an auxiliary moiety. Exemplary endosomal escape moieties include chemotherapeutics (e.g., quinolones such as chloroquine); fusogenic lipids (e.g., dioleoylphosphatidyl-ethanolamine (DOPE)); and polymers such as polyethylenimine (PEI); poly(beta-amino ester)s; polypeptides, such as polyarginines (e.g., octaarginine) and polylysines (e.g., octalysine); proton sponges, viral capsids, and peptide transduction domains as described herein. For example, fusogenic peptides can be derived from the M2 protein of influenza A viruses; peptide analogs of the influenza virus hemagglutinin; the HEF protein of the influenza C virus; the transmembrane glycoprotein of filoviruses; the transmembrane glycoprotein of the rabies virus; the transmembrane glycoprotein (G) of the vesicular stomatitis virus; the fusion protein of the Sendai virus; the transmembrane glycoprotein of the Semliki forest virus; the fusion protein of the human respiratory syncytial virus (RSV); the fusion protein of the measles virus; the fusion protein of the Newcastle disease virus; the fusion protein of the visna virus; the fusion protein of murine leukemia virus; the fusion protein of the HTLV virus; and the fusion protein of the simian immunodeficiency virus (SIV). Other moieties that can be employed to facilitate endosomal escape are described in Dominska et al., *Journal of Cell Science*, 123(8):1183-1189, 2010. Specific examples of endosomal escape moieties including moieties suitable for conjugation to the hybridized polynucleotide constructs disclosed herein are provided, e.g., in WO 2015/188197; the disclosure of these endosomal escape moieties is incorporated by reference herein.

[0169] One or more endosomal escape moieties (e.g., from 1 to 6 or from 1 to 3) can be attached to a MOIETY or X2 in formula (V', V'', V''', V''''', V''''', or V''''') through –LinkA–, as described herein.

[0170] One or more cell penetrating peptides (CPP) (e.g., from 1 to 6 or from 1 to 3) can be attached to a polynucleotide construct or a hybridized polynucleotide construct disclosed herein as an auxiliary moiety. The CPP can be linked to the hybridized polynucleotide bioreversibly through a disulfide linkage, as disclosed herein. Thus, upon delivery to a cell, the CPP can be cleaved

intracellularly, e.g., by an intracellular enzyme (e.g., protein disulfide isomerase, thioredoxin, or a thioesterase) and thereby release the polynucleotide.

[0171] CPPs are known in the art (e.g., TAT or Arg8) (Snyder and Dowdy, 2005, Expert Opin. Drug Deliv. 2, 43-51). Specific examples of CPPs including moieties suitable for conjugation to the hybridized polynucleotide constructs disclosed herein are provided, e.g., in WO 2015/188197; the disclosure of these CPPs is incorporated by reference herein.

[0172] CPPs are positively charged peptides that are capable of facilitating the delivery of biological cargo to a cell. It is believed that the cationic charge of the CPPs is essential for their function. Moreover, the transduction of these proteins does not appear to be affected by cell type, and these proteins can efficiently transduce nearly all cells in culture with no apparent toxicity (Nagahara et al., Nat. Med. 4:1449-52, 1998). In addition to full-length proteins, CPPs have also been used successfully to induce the intracellular uptake of DNA (Abu-Amer, supra), antisense polynucleotides (Astria-Fisher et al., Pharm. Res. 19:744-54, 2002), small molecules (Polyakov et al., Bioconjug. Chem. 11:762-71, 2000) and even inorganic 40 nm iron particles (Dodd et al., J. Immunol. Methods 256:89-105, 2001; Wunderbaldinger et al., Bioconjug. Chem. 13:264-8, 2002; Lewin et al., Nat. Biotechnol. 18:410-4, 2000; Josephson et al., Bioconjug. Chem. 10:186-91, 1999) suggesting that there is considerable flexibility in particle size in this process.

[0173] In one case, a CPP useful in the methods and compositions as described herein includes a peptide featuring substantial alpha-helicity. It has been discovered that transfection is optimized when the CPP exhibits significant alpha-helicity. In another case, the CPP includes a sequence containing basic amino acid residues that are substantially aligned along at least one face of the peptide. A CPP described herein may be a naturally occurring peptide or a synthetic peptide.

[0174] One or more cell penetrating peptides (e.g., from 1 to 6 or from 1 to 3) can be attached to a MOIETY or X2 in formula (I) through –LinkA–, as described herein.

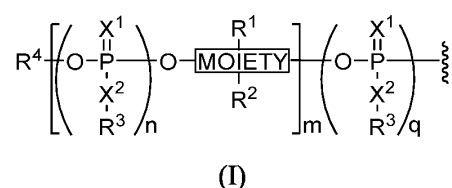
[0175] The polynucleotide constructs and the hybridized polynucleotide constructs disclosed herein can also include covalently attached neutral polymer-based auxiliary moieties. Neutral polymers include poly(C1-6 alkylene oxide), e.g., poly(ethylene glycol) and poly(propylene glycol) and copolymers thereof, e.g., di- and triblock copolymers. Other examples of polymers include esterified poly(acrylic acid), esterified poly(glutamic acid), esterified poly(aspartic acid), poly(vinyl alcohol), poly(ethylene-co-vinyl alcohol), poly(N-vinyl pyrrolidone), poly(ethyloxazoline), poly(alkylacrylates), poly(acrylamide), poly(N-alkylacrylamides), poly(N-acryloylmorpholine), poly(lactic acid), poly(glycolic acid), poly(dioxanone), poly(caprolactone), styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyurethane, N-

isopropylacrylamide polymers, and poly(N,N-dialkylacrylamides). Exemplary polymer auxiliary moieties may have molecular weights of less than 100, 300, 500, 1000, or 5000 Da (e.g., greater than 100 Da). Other polymers are known in the art.

[0176] One or more polymers (e.g., from 1 to 6 or from 1 to 3) can be attached to a MOIETY or X2 in formula (V', V'', V''', V''', V''', V''', V''') through –LinkA–, as described herein.

Conjugation Linkers

[0177] In some aspects, the polynucleic acid molecules described herein comprises a sense or antisense strand bonded to at least one group of formula (I)



or a salt thereof, or a stereoisomer thereof,

where

each X¹ is independently O or S;

each X² is independently O, S, NH, or a bond;

MOIETY is optionally substituted C₂₋₁₀ alkane-tetrayl or a group –M¹–M²–M³–, wherein each M¹ and each M³ is independently absent or optionally substituted C₁₋₆ alkylene, and M² is optionally substituted C₃₋₉ heterocycle-tetrayl, optionally substituted C₆₋₁₀ arene-tetrayl, or optionally substituted C₃₋₈ cycloalkane-tetrayl;

each R¹ and each R² is independently H, optionally substituted C₁₋₁₆ alkyl, optionally substituted C₂₋₁₆ heteroalkyl, a conjugation moiety, or –LinkA(–T)_p, provided that at least one R¹ or at least one R² is a conjugation moiety or –LinkA(–T)_p;

each R³ is independently H, optionally substituted C₁₋₁₆ alkyl, optionally substituted C₂₋₁₆ heteroalkyl, optionally substituted C₂₋₁₆ alkenyl, optionally substituted C₂₋₁₆ alkynyl, optionally substituted (C₁₋₉ heterocyclyl)-C₁₋₆-alkyl, optionally substituted (C₆₋₁₀ aryl)-C₁₋₆-alkyl, optionally substituted (C₃₋₈ cycloalkyl)-C₁₋₆-alkyl, a conjugation moiety, or –LinkA(–T)_p;

R⁴ is H, optionally substituted C₁₋₆ alkyl, –LinkA(–T)_p, or –Sol;

each LinkA is independently a multivalent linker (e.g., including –C(O)–N(H)– (e.g., at least one multivalent linker including –C(O)–N(H)– bonded to T));

each T is independently an auxiliary moiety;

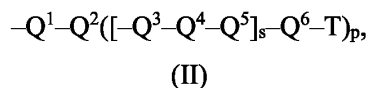
Sol is solid support;

m is an integer from 1 to 6;
 each n is independently 0 or 1;
 each p is independently an integer from 1 to 6; and
 q is an integer from 0 to 3.

The at least one group of formula (I) may be bonded to a 5'-terminus, 3'-terminus, internucleoside phosphate, internucleoside phosphorothioate, or internucleoside phosphorodithioate of the polynucleotide. When the at least one group of formula (I) is bonded to the internucleoside phosphate, internucleoside phosphorothioate, or internucleoside phosphorodithioate, q is 0. The polynucleotide construct contains no more than one Sol.

[0178] Group –LinkA– can include from 0 to 3 multivalent monomers (e.g., optionally substituted C1-6 alkane-triyl, optionally substituted C1-6 alkane-tetrayl, or trivalent nitrogen atom) and one or more divalent monomers (e.g., from 1 to 40), where each divalent monomer is independently optionally substituted C1-6 alkylene; optionally substituted C2-6 alkenylene; optionally substituted C2-6 alkynylene; optionally substituted C3-8 cycloalkylene; optionally substituted C3-8 cycloalkenylene; optionally substituted C6-14 arylene; optionally substituted C1-9 heteroarylene having 1 to 4 heteroatoms selected from N, O, and S; optionally substituted C1-9 heterocyclylene having 1 to 4 heteroatoms selected from N, O, and S; imino; optionally substituted N; O; or S(O)_m, wherein m is 0, 1, or 2. In some aspects, each monomer is independently optionally substituted C1-6 alkylene; optionally substituted C3-8 cycloalkylene; optionally substituted C3-8 cycloalkenylene; optionally substituted C6-14 arylene; optionally substituted C1-9 heteroarylene having 1 to 4 heteroatoms selected from N, O, and S; optionally substituted C1-9 heterocyclylene having 1 to 4 heteroatoms selected from N, O, and S; imino; optionally substituted N; O; or S(O)_m, where m is 0, 1, or 2 (e.g., m is 2). In certain aspects, each monomer is independently optionally substituted C1-6 alkylene; optionally substituted C3-8 cycloalkylene; optionally substituted C3-8 cycloalkenylene; optionally substituted C6-14 arylene; optionally substituted C1-9 heteroarylene having 1 to 4 heteroatoms selected from N, O, and S; optionally substituted C1-9 heterocyclylene having 1 to 4 heteroatoms selected from N, O, and S; optionally substituted N; O; or S(O)_m, where m is 0, 1, or 2 (e.g., m is 2). The non-bioreversible linker connecting the auxiliary moiety to the conjugating moiety or to the reaction product thereof can include from 2 to 500 (e.g., from 2 to 300 or from 2 to 200) of such monomers. Group –LinkA– may include a poly(alkylene oxide) (e.g., polyethylene oxide, polypropylene oxide, poly(trimethylene oxide), polybutylene oxide, poly(tetramethylene oxide), and diblock or triblock co-polymers thereof). In some aspects, the non-bioreversible linker includes polyethylene oxide (e.g., poly(ethylene oxide) having a molecular weight of less than 1 kDa).

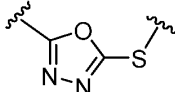
[0179] Group $-\text{LinkA}(-\text{T})_p$ in formula (I) may be prepared by a process described in the sections below. In some instances, $-\text{LinkA}(-\text{T})_p$ is of formula (II):

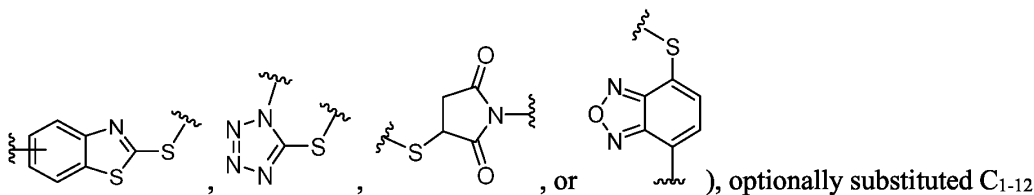


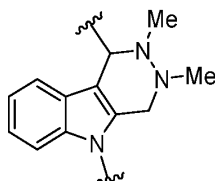
where

each s is independently an integer from 0 to 20 (e.g., from 0 to 10), where the repeating units are the same or different;

Q^1 is a conjugation linker (e.g., $[\text{Q}^3-\text{Q}^4-\text{Q}^5]_s-\text{Q}^C$, where Q^C is optionally substituted C_{2-12} heteroalkylene (e.g., a heteroalkylene containing $-\text{C}(\text{O})-\text{N}(\text{H})-$, $-\text{N}(\text{H})-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-\text{N}(\text{H})-$, or

$-\text{N}(\text{H})-\text{S}(\text{O})_2-$), optionally substituted C_{1-12} thioheterocyclylene (e.g., , or



heterocyclylene (e.g., 1,2,3-triazole-1,4-diyl or , cyclobut-3-ene-1,2-dione-3,4-diyl, or pyrid-2-yl hydrazone);

Q^2 is a linear group (e.g., $[\text{Q}^3-\text{Q}^4-\text{Q}^5]_s$), if p is 1, or a branched group (e.g., $[\text{Q}^3-\text{Q}^4-\text{Q}^5]_s-\text{Q}^7([\text{Q}^3-\text{Q}^4-\text{Q}^5]_s-(\text{Q}^7)_{p1})_{p2}$, where $p1$ is 0 or 1, $p2$ is 0, 1, 2, or 3), if p is an integer from 2 to 6;

each Q^3 and each Q^6 is independently absent, $-\text{CO}-$, $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{COO}-$, $-\text{NHC}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NHCH}_2-$, $-\text{CH}_2\text{O}-$, or $-\text{OCH}_2-$;

each Q^4 is independently absent, optionally substituted C_{1-12} alkylene, optionally substituted C_{2-12} alkenylene, optionally substituted C_{2-12} alkynylene, optionally substituted C_{2-12} heteroalkylene, optionally substituted C_{6-10} arylene, optionally substituted C_{1-9} heteroarylene, or optionally substituted C_{1-9} heterocyclylene;

each Q^5 is independently absent, $-\text{CO}-$, $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{CH}_2-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{NH}-\text{CH}(\text{R}^a)-\text{C}(\text{O})-$, or $-\text{C}(\text{O})-\text{CH}(\text{R}^a)-\text{NH}-$;

each Q^7 is independently optionally substituted C_{1-6} alkane-triyl, optionally substituted C_{1-6} alkane-tetrayl, optionally substituted C_{2-6} heteroalkane-triyl, or optionally substituted C_{2-6} heteroalkane-tetrayl; and

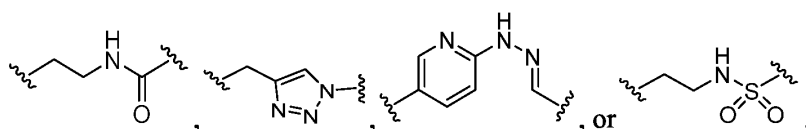
each R^a is independently H or an amino acid side chain;

provided that at least one of Q^3 , Q^4 , and Q^5 is present.

[0180] In some aspects, each Q^4 is independently absent, optionally substituted C_{1-12} alkylene, optionally substituted C_{2-12} alkenylene, optionally substituted C_{2-12} alkynylene, optionally substituted C_{2-12} heteroalkylene, or optionally substituted C_{1-9} heterocyclylene. In certain aspects, s is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0181] Thus, in formula (II), LinkA may include a single branching point, if each p1 is 0, or multiple branching points, if at least one p1 is 1.

[0182] In formula (II), Q^1 may be $-O-Q^L-Q^C-$, where Q^L is optionally substituted C_{2-12} heteroalkylene, optionally substituted C_{1-12} alkylene, or $-(\text{optionally substituted } C_{1-6} \text{ alkylene})-(\text{optionally substituted } C_{6-10} \text{ arylene})-$. In some aspects, Q^L is optionally substituted C_{2-12} heteroalkylene or optionally substituted C_{1-12} alkylene. In formula (II), Q^C may be:



[0183] In formula (II), Q^2 may be a linear group of formula $[-Q^3-Q^4-Q^5]_s-$, where Q^3 , Q^4 , and Q^5 are as defined for formula (II). Alternatively, Q^2 may be a branched group $[-Q^3-Q^4-Q^5]_s-Q^7([Q^3-Q^4-Q^5]_s-(Q^7)_{p1})_{p2}$, where each Q^7 is independently optionally substituted C_{1-6} alkane-triyl, optionally substituted C_{1-6} alkane-tetrayl, optionally substituted C_{2-6} heteroalkane-triyl, or optionally substituted C_{2-6} heteroalkane-tetrayl;

where

p1 is 0 or 1;

p2 is 0, 1, 2, or 3;

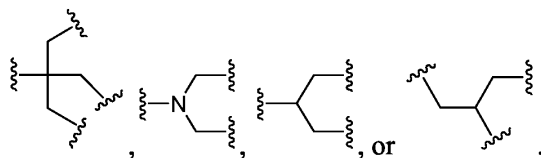
where,

when p1 is 0, LinkA is a trivalent or tetravalent linker, and,

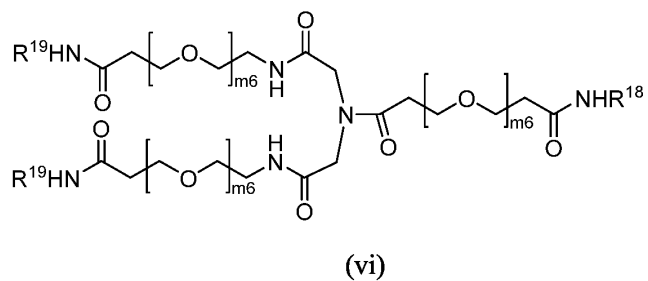
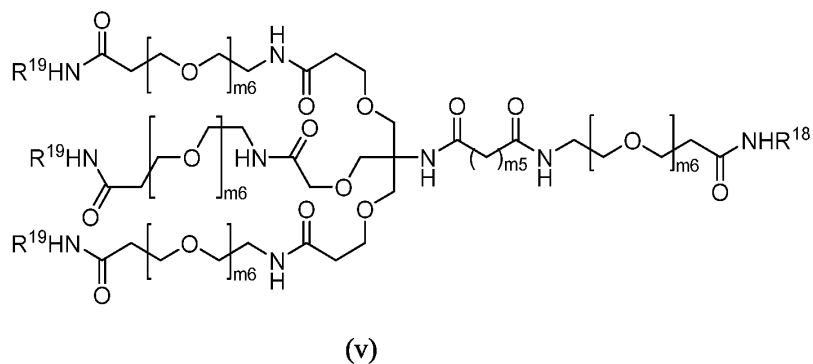
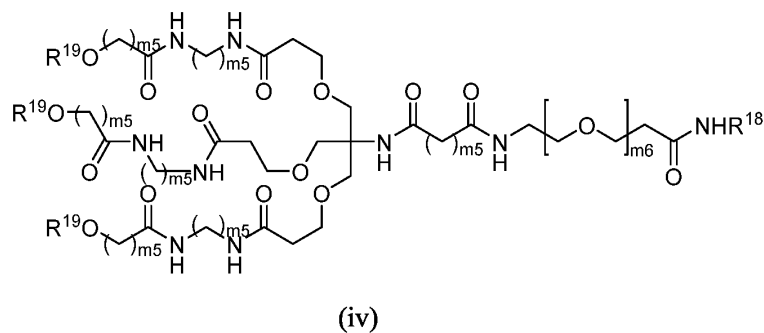
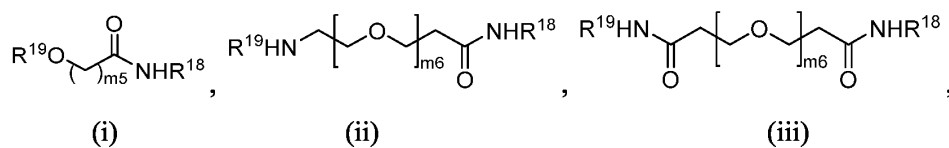
when p1 is 1, LinkA is a tetravalent, pentavalent, or hexavalent linker.

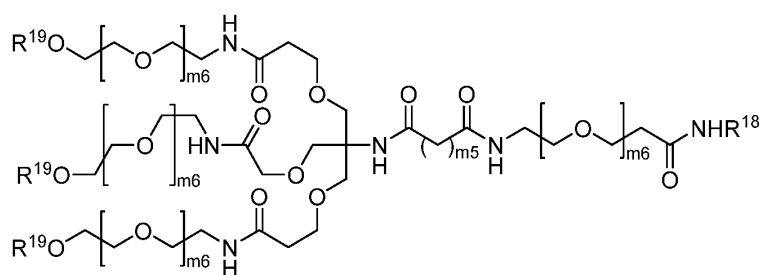
In certain aspects, p1 is 0.

In some aspects, Q^7 is:

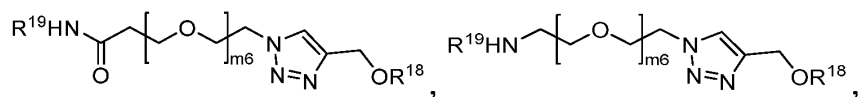


[0184] Compounds that may be used in the preparation of group –LinkA(–T)_p in formula (I) are described herein as well as in WO 2015/188197. Non-limiting examples of –LinkA include:

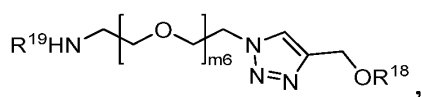




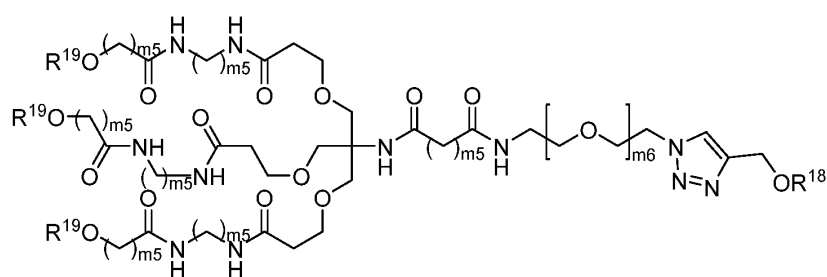
(vii)



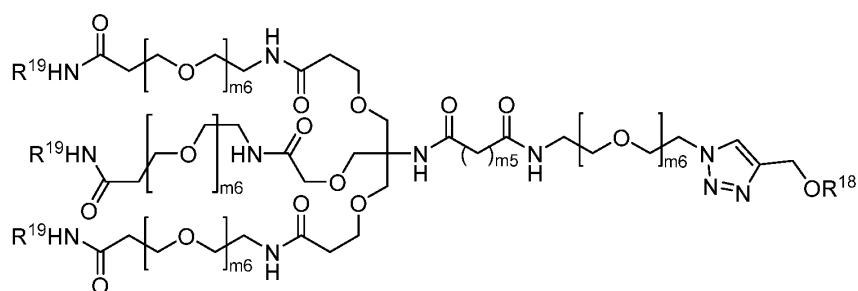
(viii)



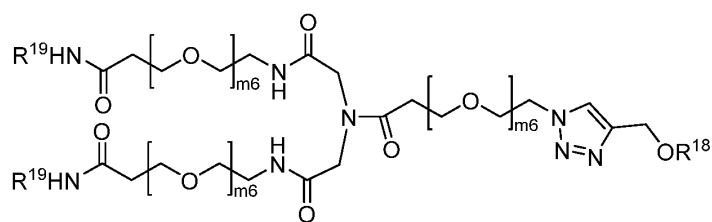
(ix)



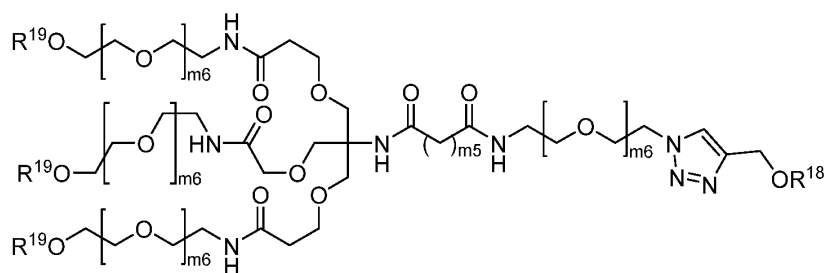
(x)



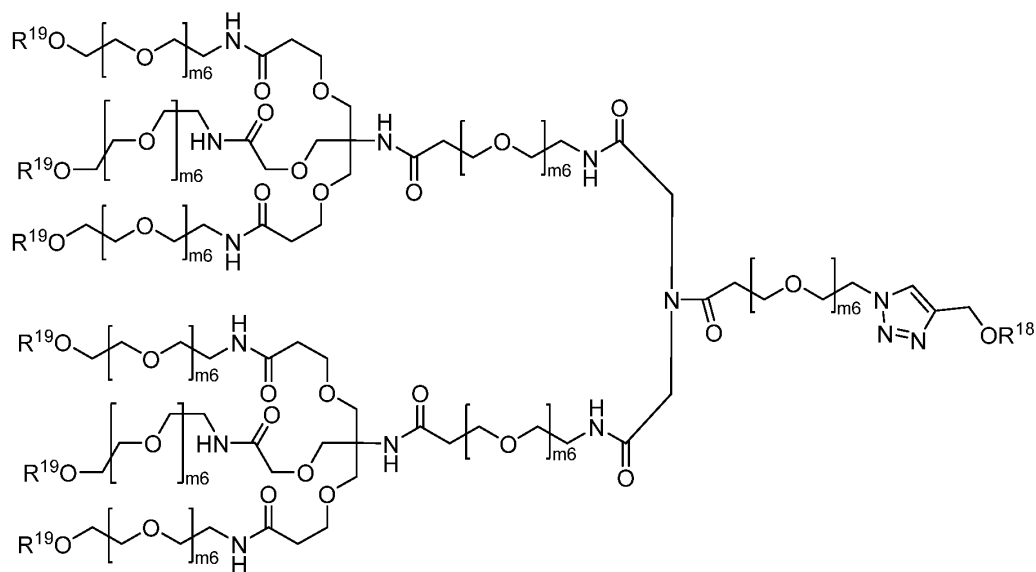
(xi)



(xii)

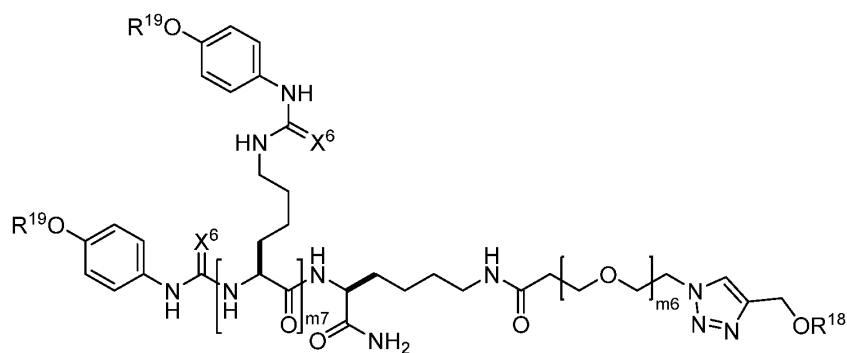


(xiii)



(xiv)

, and



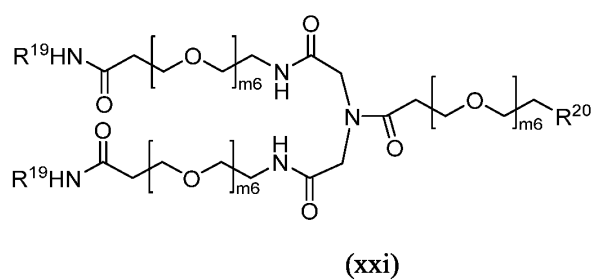
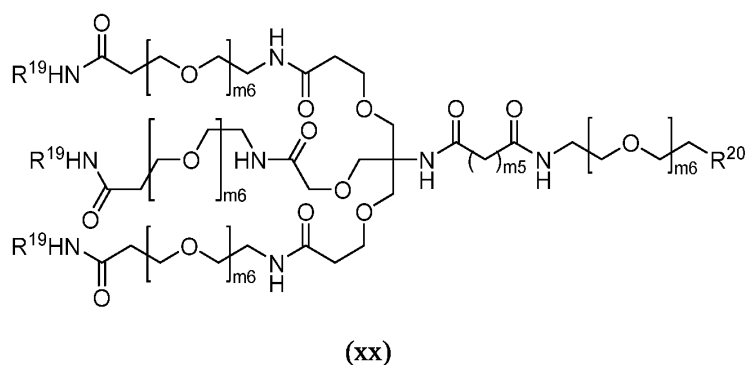
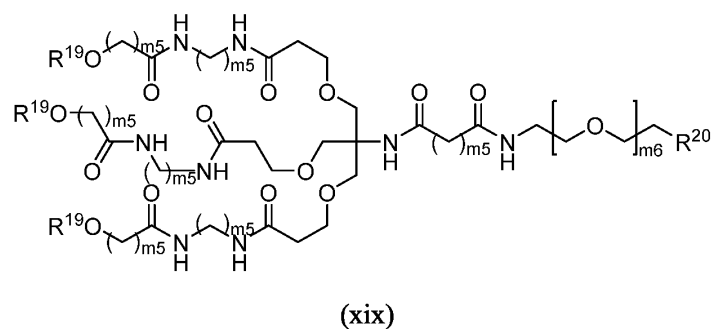
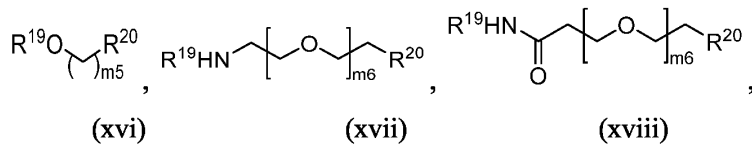
(xv)

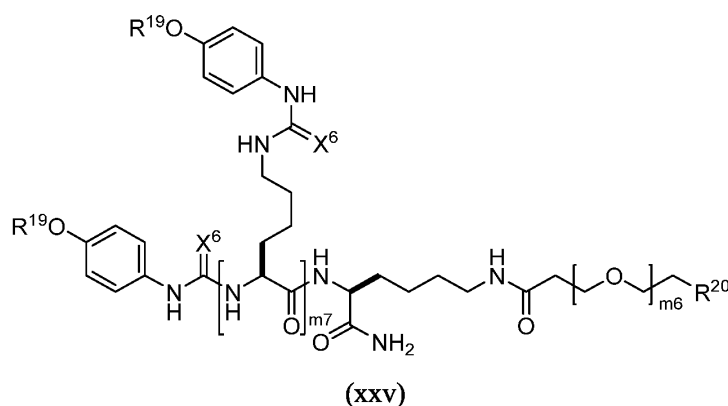
where

 R^{18} is a bond to MOIETY,each R^{19} is independently a bond to auxiliary moiety,each $m5$ is independently an integer from 1 to 20,each $m6$ is independently an integer from 1 to 10,

m7 is an integer from 1 to 6, and
each X⁶ is independently O or S.

In formula (II), when the conjugation linker is of formula $[-Q^3-Q^4-Q^5]_s-Q^C-$, $-Q^2([-Q^3-Q^4-Q^5]_s-Q^6-T)_p$ may be:





where

R^{20} is a bond to Q^C in Q^1 ,

each R^{19} is independently a bond to an auxiliary moiety,

each $m5$ is independently an integer from 1 to 20,

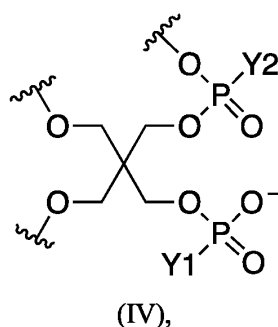
each $m6$ is independently an integer from 1 to 10,

$m7$ is an integer from 1 to 6, and

each X^6 is independently O or S.

[0185] In some aspects, the linker described herein is cleavable. In some aspects, the linker described herein is non-cleavable.

[0186] In some aspects, the polynucleic acid molecule described herein comprises a sense or antisense strand bonded to at least one group of formula (IV),

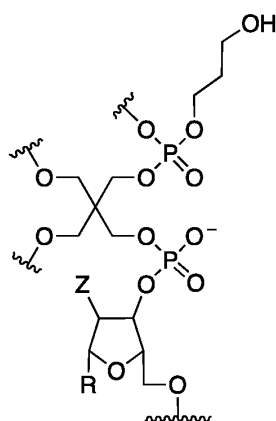


wherein at least one of $Y1$ and $Y2$ is a nucleotide from the polynucleic acid molecule.

[0187] In some instances, the $Y1$ is the last nucleotide on the 3'-terminus or the first nucleotide on the 5' terminus of one of the strands of the polynucleic acid molecule. In some instances, the $Y1$ is the last nucleotide on the 3'-terminus or the first nucleotide on the 5' terminus of the sense strand of the polynucleic acid molecule. In some instances, the $Y1$ is the last nucleotide on the 3'-terminus or the first nucleotide on the 5' terminus of the sense strand of the polynucleic acid molecule, and the $Y2$ is a 3-hydroxy-propoxy group. In some instances, the $Y2$ is the first nucleotide on the 5'-terminus or the last nucleotide on the 3'-terminus of one of the strands of the

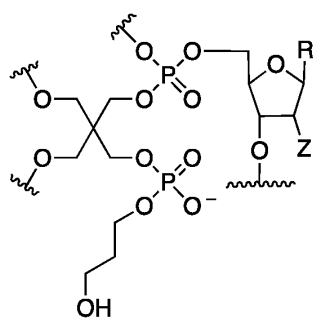
polynucleic acid molecule. In some instances, the Y2 is the first nucleotide on the 5'-terminus or the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule. In some instances, the Y2 is the first nucleotide or the last nucleotide on the 3'-terminus on the 5'-terminus of the sense strand of the polynucleic acid molecule, and the Y1 is a 3-hydroxy-propoxy group. In other instances, the Y1 and Y2 are two consecutive nucleotides in one of the strands of the polynucleic acid molecule.

[0188] In some aspects, the targeting moiety described herein is conjugated to 3' end of the sense strand (e.g., formula (IV') or (IV''')). In some aspects, the targeting moiety described herein is conjugated to 5' end of the sense strand (e.g., formula (IV'') or (IV''')). In some aspects, the targeting moiety described herein is conjugated to 3' end of the antisense strand (e.g., formula (IV') or (IV''')). In some aspects, the targeting moiety described herein is conjugated to 5' end of the antisense strand (e.g., formula (IV'') or (IV''')).



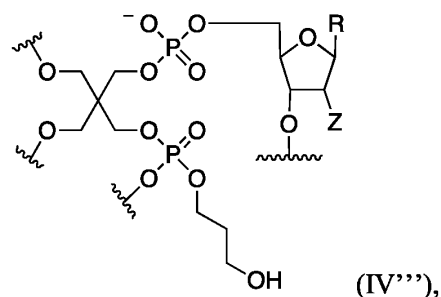
(IV')

wherein Z in formula (IV') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (IV') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

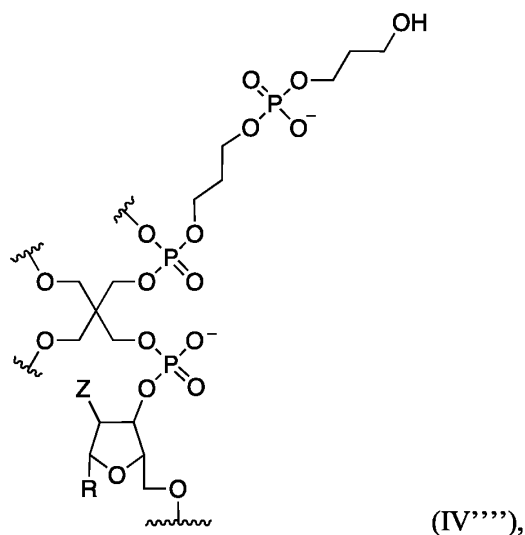


(IV''),

wherein Z in formula (IV'') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (IV'') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



wherein Z in formula (IV''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (IV''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



wherein Z in formula (IV''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (IV''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

Pharmaceutical Compositions

[0189] Delivery of the polynucleotide molecules described herein can be achieved by contacting a cell with the polynucleotide molecules using a variety of methods. In particular aspects, the polynucleotide molecule described herein is formulated with various excipients, vehicles, and carriers, as described more fully elsewhere herein.

[0190] A pharmaceutical composition described herein can be prepared to include a hybridized polynucleotide construct disclosed herein, into a form suitable for administration to a subject using

carriers, excipients, and vehicles. Frequently used excipients include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol, and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial, anti-oxidants, chelating agents, and inert gases. Other pharmaceutically acceptable vehicles include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005), and The United States Pharmacopeia: The National Formulary (USP 36 NF31), published in 2013. The pH and exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. See Goodman and Gilman's, The Pharmacological Basis for Therapeutics.

[0191] The pharmaceutical compositions described herein may be administered locally or systemically. The therapeutically effective amounts will vary according to factors, such as the degree of infection in a subject, the age, sex, and weight of the individual. Dosage regimes can be adjusted to provide the optimum therapeutic response. For example, several divided doses can be administered daily or the dose can be proportionally reduced as indicated by the exigencies of the therapeutic situation.

[0192] The pharmaceutical composition can be administered in a convenient manner, such as by injection (e.g., subcutaneous, intravenous, intraorbital, and the like), oral administration, ophthalmic application, inhalation, topical application, or rectal administration. Depending on the route of administration, the pharmaceutical composition can be coated with a material to protect the pharmaceutical composition from the action of enzymes, acids, and other natural conditions that may inactivate the pharmaceutical composition. The pharmaceutical composition can also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

[0193] 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 dispersions. The composition will typically be sterile and fluid to the extent that easy syringability exists. Typically the composition will be stable under the conditions of manufacture and storage and preserved against the contaminating action of microorganisms, such as bacteria and fungi. The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene

glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size, in the case of dispersion, and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, isotonic agents, for example, sugars, polyalcohols, such as mannitol, sorbitol, or sodium chloride are used in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

[0194] Sterile injectable solutions can be prepared by incorporating the pharmaceutical composition in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the pharmaceutical composition into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above.

[0195] It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein, refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of pharmaceutical composition is calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specification for the dosage unit forms is related to the characteristics of the pharmaceutical composition and the particular therapeutic effect to be achieved. The principal pharmaceutical composition is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable vehicle in an acceptable dosage unit. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the ingredients.

[0196] The pharmaceutical composition can be orally administered, for example, in a carrier, e.g., in an enteric-coated unit dosage form. The pharmaceutical composition and other ingredients can also be enclosed in a hard or soft-shell gelatin capsule or compressed into tablets. For oral therapeutic administration, the pharmaceutical composition can be incorporated with excipients and used in the form of ingestible tablets, troches, capsules, pills, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations can, of course, be varied and can conveniently be between about 5% to about 80% of the weight of the unit. The tablets, troches, pills, capsules, and

the like can also contain the following: a binder, such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid, and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin, or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier. Various other materials can be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules can be coated with shellac, sugar, or both. A syrup or elixir can contain the agent, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring, such as cherry or orange flavor. Any material used in preparing any dosage unit form should be of pharmaceutically acceptable purity and substantially non-toxic in the amounts employed. In addition, the pharmaceutical composition can be incorporated into sustained-release preparations and formulations.

[0197] The pharmaceutical composition described herein may comprise one or more permeation enhancer that facilitates bioavailability of the polynucleotide molecule described herein. WO 2000/67798, Muranishi, 1990, Crit. Rev. Ther. Drug Carrier Systems, 7, 1, Lee *et al.*, 1991, Crit. Rev. Ther. Drug Carrier Systems, 8, 91 are herein incorporated by reference in its entirety. In some aspects, the permeation enhancer is intestinal. In some aspects, the permeation enhancer is transdermal. In some aspects, the permeation enhancer is to facilitate crossing the brain-blood barrier. In some aspects, the permeation enhancer improves the permeability in the oral, nasal, buccal, pulmonary, vaginal, or corneal delivery model. In some aspects, the permeation enhancer is a fatty acid or a derivative thereof. In some aspects, the permeation enhancer is a surfactant or a derivative thereof. In some aspects, the permeation enhancer is a bile salt or a derivative thereof. In some aspects, the permeation enhancer is a chelating agent or a derivative thereof. In some aspects, the permeation enhancer is a non-chelating non-surfactant or a derivative thereof. In some aspects, the permeation enhancer is an ester or a derivative thereof. In some aspects, the permeation enhancer is an ether or a derivative thereof. In some aspects, the permeation enhancer is arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof. In one specific aspect, the permeation enhancer is sodium caprate (C10). In some aspects, the permeation enhancer is chenodeoxycholic acid (CDCA), ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate or sodium

glycodihydrofusidate. In some aspects, the permeation enhancer is polyoxyethylene-9-lauryl ether, or polyoxyethylene-20-cetyl ether.

[0198] For the polynucleotide molecule described herein, suitable pharmaceutically acceptable salts include (i) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (ii) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like; and (iii) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like.

[0199] While the hybridized polynucleotide constructs described herein may not require the use of excipients for delivery to the target cell, the use of excipients may be advantageous in some aspects. Thus, for delivery to the target cell, the hybridized polynucleotide molecule described herein can non-covalently bind an excipient to form a complex. The excipient can be used to alter biodistribution after delivery, to enhance uptake, to increase half-life or stability of the strands in the hybridized polynucleotide constructs (e.g., improve nuclease resistance), and/or to increase targeting to a particular cell or tissue type.

[0200] Exemplary excipients include a condensing agent (e.g., an agent capable of attracting or binding a nucleic acid through ionic or electrostatic interactions); a fusogenic agent (e.g., an agent capable of fusing and/or being transported through a cell membrane); a protein to target a particular cell or tissue type (e.g., thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, or any other protein); a lipid; a lipopolysaccharide; a lipid micelle or a liposome (e.g., formed from phospholipids, such as phosphatidylcholine, fatty acids, glycolipids, ceramides, glycerides, cholesterol, or any combination thereof); a nanoparticle (e.g., silica, lipid, carbohydrate, or other pharmaceutically-acceptable polymer nanoparticle); a polyplex formed from cationic polymers and an anionic agent (e.g., a CRO), where exemplary cationic polymers include polyamines (e.g., polylysine, polyarginine, polyamidoamine, and polyethylene imine); cholesterol; a dendrimer (e.g., a polyamidoamine (PAMAM) dendrimer); a serum protein (e.g., human serum albumin (HSA) or low-density lipoprotein (LDL)); a carbohydrate (e.g., dextran, pullulan, chitin, chitosan, inulin, cyclodextrin, or hyaluronic acid); a lipid; a synthetic polymer, (e.g., polylysine (PLL), polyethylenimine, poly-L-aspartic acid, poly-L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolic) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl

alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymer, pseudopeptide-polyamine, peptidomimetic polyamine, or polyamine); a cationic moiety (e.g., cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or alpha helical peptide); a multivalent sugar (e.g., multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine, multivalent mannose, or multivalent fucose); a vitamin (e.g., vitamin A, vitamin E, vitamin K, vitamin B, folic acid, vitamin B12, riboflavin, biotin, or pyridoxal); a cofactor; or a drug to disrupt cellular cytoskeleton to increase uptake (e.g., taxol, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin).

[0201] Other therapeutic agents as described herein may be included in a pharmaceutical composition described herein in combination with a polynucleotide molecule described herein.

Methods of Treatment

[0202] In some aspects, described herein is a method of modulating expression of Lp(a) gene in a subject, comprising: administering to the subject a polynucleic acid molecule described herein, a polynucleic acid molecule conjugate described herein, or a pharmaceutical composition described herein, thereby modulating the expression of Lp(a) gene in the subject.

[0203] In some aspects, the method described herein reduces expression of Lp(a) gene (e.g., expression of Lp(a) mRNA) in a subject by about or at least 10% compared to a control. The term “control” as used herein refers to a subject or a cell receiving no treatment or placebo. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 20% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 30% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 40% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 50% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 60% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 70% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 80% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about or at least 90% compared to a control. In some aspects, the method described herein reduces expression of Lp(a) gene in a subject by about 100% compared to a control.

IC50 value of about 35 μM . In some aspects, the method described herein achieves an IC50 value of about 40 μM . In some aspects, the method described herein achieves an IC50 value of about 50 μM . In some aspects, the method described herein achieves an IC50 value of about 60 μM . In some aspects, the method described herein achieves an IC50 value of about 80 μM . In some aspects, the method described herein achieves an IC50 value of about 100 μM . In some aspects, the method described herein achieves an IC50 value of about 120 μM . In some aspects, the method described herein achieves an IC50 value of about 160 μM .

[0206] In some aspects, described herein is a method of modulating plasma Lp(a) level in a subject in need thereof, comprising administering to the subject a polynucleic acid molecule described herein, a polynucleic acid molecule conjugate described herein, or a pharmaceutical composition described herein, wherein the polynucleic acid molecule described herein, the polynucleic acid molecule conjugate described herein, or the pharmaceutical composition described herein reduces the plasma Lp(a) level in the subject.

[0207] In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 10% compared to a control (e.g., untreated subject or a subject before the treatment). In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 20% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 30% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 40% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 50% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 60% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 70% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 80% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about or at least 90% compared to a control. In some aspects, the method described herein reduces plasma Lp(a) level in a subject by about 100% compared to a control.

[0208] In some aspects, described herein is a method for treating or preventing a Lp(a) related disorder or symptoms thereof, cardiovascular disease or a lipid disorder, comprising administering to the subject a polynucleic acid molecule as disclosed herein, a polynucleic acid molecule conjugate as disclosed herein, or a pharmaceutical composition as disclosed herein.

[0209] In some aspects, the Lp(a) related disorder or cardiovascular disease includes coronary artery disease, acute myocardial infarction, asymptomatic carotid atherosclerosis, stroke, atrial

fibrillation, or peripheral artery occlusive disease. In some aspects, the cardiovascular disease is hypercholesterolemia. In some aspects, the cardiovascular disease is myocardial infarction. In some aspects, the cardiovascular disease is the stroke. In some aspects, the cardiovascular disease is calcific aortic valve stenosis. In some aspects, the cardiovascular disease is cardiac arrest. In some aspects, the cardiovascular disease is peripheral arterial disease. In some aspects, the lipid disorder is hyperlipidemia or hypercholesterolemia.

Combination Therapy

[0210] In some instances, the methods as disclosed herein comprises administering a polynucleic acid molecule as disclosed herein, a polynucleic acid molecule conjugate as disclosed herein, or a pharmaceutical composition as disclosed herein to a subject (e.g., a human patient) who is on a therapeutic regime for the treatment of Lp(a) related disorder or CVD at the time of, or just prior to, administration of the polynucleic acid molecule as disclosed herein, a polynucleic acid molecule conjugate as disclosed herein, or a pharmaceutical composition as disclosed herein. For example, a patient who has previously been diagnosed with atherosclerosis may have been prescribed and is taking a stable therapeutic regimen of another drug prior to and/or concurrent with administration of a polynucleic acid molecule as disclosed herein, a polynucleic acid molecule conjugate as disclosed herein, or a pharmaceutical composition as disclosed herein. The prior or concurrent therapeutic regimen can comprise, for example, (1) an agent which induces a cellular depletion of cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase, such as a statin (e.g., cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, etc.); (2) an agent which inhibits cholesterol uptake and or bile acid re-absorption; (3) an agent which increase lipoprotein catabolism (such as niacin); and/or (4) activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol.

Patient Population

[0211] The methods disclosed herein are useful for reducing plasma Lp(a) levels in subjects that exhibit an elevated level of plasma Lp(a). The subject can be human or non-human primates. In some instances, the subject is otherwise healthy except for exhibiting elevated serum Lp(a). For example, the subject may not exhibit any other risk factor of cardiovascular, thrombotic or other diseases or disorders at the time of treatment. In other instances, however, the subject is selected on the basis of being diagnosed with, or at risk of developing, a disease or disorder that is caused by or correlated with elevated plasma Lp(a). For instance, at the time of, or prior to administration of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein, the subject may be diagnosed with

or identified as being at risk of developing a cardiovascular disease or disorder, such as, e.g., coronary artery disease, acute myocardial infarction, asymptomatic carotid atherosclerosis, stroke, atrial fibrillation, peripheral artery occlusive disease, etc. The cardiovascular disease or disorder, in some instances, is hypercholesterolemia. For example, a subject may be selected for treatment with the methods as disclosed herein if the subject is diagnosed with or identified as being at risk of developing a hypercholesterolemia condition such as, e.g., heterozygous Familial Hypercholesterolemia (heFH), homozygous Familial Hypercholesterolemia (hoFH), as well as incidences of hypercholesterolemia that are distinct from Familial Hypercholesterolemia (nonFH). The subject may be diagnosed with or identified as being at risk of developing a lipid disease or disorder, such as, e.g., hyperlipidemia and hypercholesterolemia.

[0212] In some instances, at the time of, or prior to administration of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein, the subject may be diagnosed with or identified as being at risk of developing a thrombotic occlusive disease or disorder, such as, e.g., pulmonary embolism, central retinal vein occlusion, etc. The patient can be selected on the basis of being diagnosed with or at risk of developing a combination of two or more of the abovementioned diseases or disorders. For example, at the time of, or prior to administration of the pharmaceutical composition of the present invention, the subject may be diagnosed with or identified as being at risk of developing coronary artery disease and pulmonary embolism. Other diagnostic combinations (e.g., atherosclerosis and central retinal vein occlusion, heFH and stroke, etc.) are also included in the definition of the patient populations that are treatable by the methods as disclosed herein.

[0213] In some instances, the subject to be treated with the methods as disclosed herein is selected on the basis of one or more factors selected from the group consisting of age (e.g., older than 40, 45, 50, 55, 60, 65, 70, 75, or 80 years), race, gender (male or female), exercise habits (e.g., regular exerciser, non-exerciser), other preexisting medical conditions (e.g., type-II diabetes, high blood pressure, etc.), and current medication status (e.g., currently taking statins (e.g., cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, etc.), beta blockers, niacin, etc.). The present disclosure also provides methods for reducing plasma Lp(a) levels in patients who are intolerant of, non-responsive to, or inadequately responsive to conventional statin therapy. Potential patients can be selected/screened on the basis of one or more of these factors (e.g., by questionnaire, diagnostic evaluation, etc.) before being treated with the methods as disclosed herein.

Dosage

[0214] The amount of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein administered to a subject according to the methods as disclosed herein is, generally, a therapeutically effective amount. As used herein, the term “therapeutically effective amount” refers to a dose of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein that results in a detectable reduction in plasma Lp(a). For example, a therapeutically effective amount of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein includes, for example, an amount of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein that causes a reduction of at least 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, or more in plasma Lp(a) levels when administered to a subject. In some instances, a therapeutically effective amount of the polynucleic acid molecule as disclosed herein can a dose that can cause a reduction of at least 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, or more in Lp(a) mRNA levels when administered to a subject.

Regimens

[0215] The polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein can be administered to a subject over a defined time course. The methods disclosed herein can comprise sequentially administering to a subject multiple doses of the polynucleic acid molecule as disclosed herein, the polynucleic acid molecule conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein. As used herein, “sequentially administering” means that each dose of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present disclosure provides methods which comprise sequentially administering to the patient a single initial dose of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition, followed by one or more secondary doses of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition, and optionally followed by one or more tertiary doses of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition.

[0216] The terms “initial dose,” “secondary doses,” and “tertiary doses,” refer to the temporal sequence of administration of the polynucleic acid molecule, the polynucleic acid molecule

conjugate, or the pharmaceutical composition. Thus, the “initial dose” is the dose which is administered at the beginning of the treatment regimen (also referred to as the “baseline dose”); the “secondary doses” are the doses which are administered after the initial dose; and the “tertiary doses” are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses can all contain the same amount of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition, but will generally differ from one another in terms of frequency of administration. In some instances, the amount of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

[0217] In some instances, each secondary and/or tertiary dose is administered 1 to 30 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more) days after the immediately preceding dose. The phrase “the immediately preceding dose,” as used herein, means, in a sequence of multiple administrations, the dose of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0218] The methods as disclosed herein can comprise administering to a patient any number of secondary and/or tertiary doses of the polynucleic acid molecule, the polynucleic acid molecule conjugate, or the pharmaceutical composition. For example, in some instances, only a single secondary dose is administered to the patient. In other instances, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. In some instances, only a single tertiary dose is administered to the patient. In other instances, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0219] Where multiple secondary doses are administered, each secondary dose can be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 29 days after the immediately preceding dose. Similarly, where multiple tertiary doses are administered, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 1 to 60 days after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

EXEMPLARY EMBODIMENTS

[0220] Embodiment 1. A polynucleic acid molecule for modulating expression of lipoprotein(a) (Lp(a)) gene, comprising a nucleic acid sequence that is at least 80%, at least 85%, at least 90% identical to a nucleic acid sequence selected from Table 1, Table 2, or Table 5.

[0221] Embodiment 2. The polynucleic acid molecule of embodiment [0220], wherein the polynucleic acid molecule comprises a nucleic acid sequence selected from Table 1, Table 2, or Table 5.

[0222] Embodiment 3. The polynucleic acid molecule of any one of embodiments 1-2, wherein the polynucleic acid molecule is a single-stranded nucleic acid molecule.

[0223] Embodiment 4. The polynucleic acid molecule of embodiment 3, wherein the single-stranded nucleic acid molecule comprises at least 14, 15, 16, 17, 18 consecutive nucleotides that are complementary to a nucleic acid sequence selected from SEQ ID NOs: 309-462, with no more than 1, 2, 3, 4 mismatches.

[0224] Embodiment 5. The polynucleic acid molecule of embodiment 3, wherein the single-stranded nucleic acid molecule comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 1-154.

[0225] Embodiment 6. The polynucleic acid molecule of embodiment [0220] or 2, wherein the polynucleic acid molecule is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand.

[0226] Embodiment 7. The polynucleic acid molecule of embodiment 5, wherein the sense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 309-462.

[0227] Embodiment 8. The polynucleic acid molecule of embodiment 5 or embodiment 6, wherein the antisense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 1-154.

[0228] Embodiment 9. The polynucleic acid molecule of embodiment 5, wherein the sense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, or 20 consecutive sequences from a nucleic acid sequence selected from SEQ ID NOs: 309-462, with no more than 1, 2, 3, or 4 mismatches.

[0229] Embodiment 10. The polynucleic acid molecule of embodiment [0225], wherein the antisense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, 20,

21, or 22 consecutive sequences of a nucleic acid sequence selected from SEQ ID NOs: 1-154, with no more than 1, 2, 3, or 4 mismatches.

[0230] Embodiment 11. The polynucleic acid molecule of any one of embodiments [0225]-[0229], wherein the sense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 309-462 and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 1-154.

[0231] Embodiment 12. The polynucleic acid molecule of any one of embodiments [0220]-[0230], wherein the polynucleic acid molecule comprises (1) a 2'-fluoro modified nucleotide; (2) a 2'-O-methyl modified nucleotide; or (3) a modified internucleotide linkage.

[0232] Embodiment 13. The polynucleic acid molecule of any one of embodiments [0225]-12, wherein the sense strand comprises at least two consecutive modified internucleotide linkages at the 5' end.

[0233] Embodiment 14. The polynucleic acid molecule of any one of embodiments 6-13, wherein the antisense strand comprises at least two consecutive modified internucleotide linkages at the 5' end and/or 3' end.

[0234] Embodiment 15. The polynucleic acid molecule of any one of embodiments 6-14, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', wherein n stands for a 2'-O-methyl modified nucleotide, and wherein Nf stands for a 2'-fluoro modified nucleotide.

[0235] Embodiment 16. The polynucleic acid molecule of any one of embodiments [0231]-[0234], wherein the modified internucleotide linkage is a phosphorothioate linkage.

[0236] Embodiment 17. The polynucleic acid molecule of embodiment [0235], wherein the modified internucleotide linkage comprises a stereochemically enriched phosphorothioate internucleotide linkage.

[0237] Embodiment 18. The polynucleic acid molecule of any one of embodiments [0231]-17, wherein the modified internucleotide linkage is an SP chiral internucleotide phosphorothioate linkage.

[0238] Embodiment 19. The polynucleic acid molecule of embodiment [0237], wherein the polynucleic acid comprises a plurality of modified internucleotide linkages, and at least 1, 2, 3, or 4 of the plurality of modified internucleotide linkages are stereochemically enriched phosphorothioate internucleotide linkages.

[0239] Embodiment 20. The polynucleic acid molecule of embodiment [0238], wherein the stereochemically enriched phosphorothioate internucleotide linkages comprise both R- and S-isomers.

[0240] Embodiment 21. The polynucleic acid molecule of embodiment [0238] or [0239], wherein the at least one stereochemically enriched phosphorothioate is disposed between two consecutive nucleosides that are two of six 5' or 3'-terminal nucleosides of the sense strand or the antisense strand.

[0241] Embodiment 22. The polynucleic acid molecule of any one of embodiments [0225]-[0240], wherein the sense strand or antisense strand is 19-25, or 21-23 nucleotides in length.

[0242] Embodiment 23. The polynucleic acid molecule of embodiments [0220]-[0224], wherein the polynucleic acid molecule is 19-25 or 21-23 nucleotides in length.

[0243] Embodiment 24. The polynucleic acid molecule of any one of embodiments 1-23, wherein the sense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 463-616.

[0244] Embodiment 25. The polynucleic acid molecule of any one of embodiments 1-24, wherein the antisense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 155-308.

[0245] Embodiment 26. The polynucleic acid molecule of any one of embodiments 1-25, wherein the sense strand comprises a sequence selected from a nucleic acid sequence of SEQ ID NOs: 463-616, and the antisense strand comprises a sequence selected from a nucleic acid sequence of SEQ ID NOs: 155-308.

[0246] Embodiment 27. A polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises :

(a) an antisense strand comprising the nucleotide sequence of

UAGAUGACCAAGCUUGGCAGGUC (SEQ ID NO: 4) and a sense strand comprising the nucleotide sequence of CCUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 312);

(b) an antisense strand comprising the nucleotide sequence of

UAUAGAUGACCAAGCUUGGCAGG (SEQ ID NO: 5) and a sense strand comprising the nucleotide sequence of UGCCAAGCUUGGUCAUCUAUA (SEQ ID NO: 313);

(c) an antisense strand comprising the nucleotide sequence of

UCAUAGAUGACCAAGCUUGGCAG (SEQ ID NO: 6) and a sense strand comprising the nucleotide sequence of GCCAAGCUUGGUCAUCUAUGA (SEQ ID NO: 314);

(d) an antisense strand comprising the nucleotide sequence of

UCGACGGCAGUCCCUUCUGCGUC (SEQ ID NO: 11) and a sense strand comprising the nucleotide sequence of CGCAGAAGGGACUGCCGUCGA (SEQ ID NO: 319);

- (e) an antisense strand comprising the nucleotide sequence of UUCUAGGCUUGGAACCGGGGUA (SEQ ID NO: 18) and a sense strand comprising the nucleotide sequence of ACCCCGGUCCAAGCCUAGAA (SEQ ID NO: 326);
- (f) an antisense strand comprising the nucleotide sequence of UAGCCUCUAGGCUUGGAACCGGG (SEQ ID NO: 21) and a sense strand comprising the nucleotide sequence of CGGUCCAAGCCUAGAGGCUA (SEQ ID NO: 329);
- (g) an antisense strand comprising the nucleotide sequence of UUUACCGUGGUAGCACUCCUGCA (SEQ ID NO: 44) and a sense strand comprising the nucleotide sequence of CAGGAGUGCUACCACGGUAAA (SEQ ID NO: 352);
- (h) an antisense strand comprising the nucleotide sequence of UUGUCCAUAACCGUGGUAGCACU (SEQ ID NO: 47) and a sense strand comprising the nucleotide sequence of UGCUACCACGGUAAUGGACAA (SEQ ID NO: 355);
- (i) an antisense strand comprising the nucleotide sequence of UCUCUGUCCAUAACCGUGGUAGC (SEQ ID NO: 49) and a sense strand comprising the nucleotide sequence of UACCACGGUAAUGGACAGAGA (SEQ ID NO: 357);
- (j) an antisense strand comprising the nucleotide sequence of UAUUGUGUCAGGUUGCAGUACUC (SEQ ID NO: 60) and a sense strand comprising the nucleotide sequence of GUACUGCAACCUGACACAAUA (SEQ ID NO: 368);
- (k) an antisense strand comprising the nucleotide sequence of UUGCGUCUGAGCAUUGUGUCAGG (SEQ ID NO: 64) and a sense strand comprising the nucleotide sequence of UGACACAAUGCUCAGACGCAA (SEQ ID NO: 372);
- (l) an antisense strand comprising the nucleotide sequence of UUAACUCUGUCCAUAUUGGUAGU (SEQ ID NO: 88) and a sense strand comprising the nucleotide sequence of UACCAUUAUGGACAGAGUUA (SEQ ID NO: 396);
- (m) an antisense strand comprising the nucleotide sequence of UCCAAGCUUGGCAAGUUCUCCU (SEQ ID NO: 89) and a sense strand comprising the nucleotide sequence of GAAGAACUUGCCAAGCUUGGA (SEQ ID NO: 397);
- (n) an antisense strand comprising the nucleotide sequence of UAGAUGACCAAGCUUGGCAAGUU (SEQ ID NO: 90) and a sense strand comprising the nucleotide sequence of CUUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 398); or
- (o) an antisense strand comprising the nucleotide sequence of UGGUCCGACUAUGCUGGUGUGGU (SEQ ID NO: 98) and a sense strand comprising the nucleotide sequence of CACACCAGCAUAGUCGGACCA (SEQ ID NO: 406).

[0247] Embodiment 28. A polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises:

- (a) an antisense strand comprising the nucleotide sequence of usAfsgaugAfccaaGfcUfuGfgcaggsusc (SEQ ID NO: 158) and a sense strand comprising the nucleotide sequence of cscsugccAfaGfcUfuggucauca (SEQ ID NO: 466);
- (b) an antisense strand comprising the nucleotide sequence of usAfsuagaUfgaccAfaGfcUfuggcasgsg (SEQ ID NO: 159) and a sense strand comprising the nucleotide sequence of usgsccaaGfcUfuGfgucaucaua (SEQ ID NO: 467);
- (c) an antisense strand comprising the nucleotide sequence of usCfsauagAfugacCfaAfgCfuuggcsasg (SEQ ID NO: 160) and a sense strand comprising the nucleotide sequence of gscscaagCfuUfgGfucaucauga (SEQ ID NO: 468);
- (d) an antisense strand comprising the nucleotide sequence of usCfsgacgGfcaguCfcCfuUfcugcgsusc (SEQ ID NO: 165) and a sense strand comprising the nucleotide sequence of csgscagaAfgGfgAfcugccgucga (SEQ ID NO: 473);
- (e) an antisense strand comprising the nucleotide sequence of usUfscuagGfcuugGfaAfcCfggggusasa (SEQ ID NO: 172) and a sense strand comprising the nucleotide sequence of ascscgccGfuUfcCfaagccuagaa (SEQ ID NO: 480);
- (f) an antisense strand comprising the nucleotide sequence of usAfsgccuCfuaggCfuUfgGfaaccgsgsg (SEQ ID NO: 175) and a sense strand comprising the nucleotide sequence of csgsguucCfaAfgCfcuagaggcua (SEQ ID NO: 483);
- (g) an antisense strand comprising the nucleotide sequence of usUfsuaccGfugguAfgCfaCfuccugscsa (SEQ ID NO: 198) and a sense strand comprising the nucleotide sequence of csasggagUfgCfuAfcacgguaaa (SEQ ID NO: 506);
- (h) an antisense strand comprising the nucleotide sequence of usUfsguccAfuuacCfgUfgGfuagcascu (SEQ ID NO: 201) and a sense strand comprising the nucleotide sequence of usgscuacCfaCfgGfuauaggacaa (SEQ ID NO: 509);
- (i) an antisense strand comprising the nucleotide sequence of usCfsucugUfccauUfaCfcGfugguasgsc (SEQ ID NO: 203) and a sense strand comprising the nucleotide sequence of usascacGfgUfaAfuggacagaga (SEQ ID NO: 511);
- (j) an antisense strand comprising the nucleotide sequence of usAfsuuguGfucagGfuUfgCfaguacsusc (SEQ ID NO: 214) and a sense strand comprising the nucleotide sequence of gsusacugCfaAfcCfugacacaaua (SEQ ID NO: 522);

(k) an antisense strand comprising the nucleotide sequence of usUfsgcguCfugagCfaUfuGfugucasgsg (SEQ ID NO: 218) and a sense strand comprising the nucleotide sequence of usgsacacAfaUfgCfucagacgcaa (SEQ ID NO: 526);

(l) an antisense strand comprising the nucleotide sequence of usUfsaacuCfugucCfaUfaAfugguasgsu (SEQ ID NO: 242) and a sense strand comprising the nucleotide sequence of usasccauUfaUfgGfacagaguuaa (SEQ ID NO: 550);

(m) an antisense strand comprising the nucleotide sequence of usCfscaagCfuuggCfaAfgUfucuucscsu (SEQ ID NO: 243) and a sense strand comprising the nucleotide sequence of gsaagaaCfuUfgCfcaagcuugga (SEQ ID NO: 551);

(n) an antisense strand comprising the nucleotide sequence of usAfsgaugAfccaaGfcUfuGfgcaagsusu (SEQ ID NO: 244) and a sense strand comprising the nucleotide sequence of csusugccAfaGfcUfuggucaucua (SEQ ID NO: 552); or

(o) an antisense strand comprising the nucleotide sequence of usGfsguccGfacuaUfgCfuGfgugugsgsu (SEQ ID NO: 252) and a sense strand comprising the nucleotide sequence of csascaccAfgCfaUfagucggacca (SEQ ID NO: 560),

wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

[0248] Embodiment 29. A polynucleic acid molecule conjugate for modulating expression of lipoprotein(a) gene (Lp(a)), wherein the polynucleic acid molecule conjugate comprises a polynucleic acid molecule of any one of embodiments [0220]-23 and an asialoglycoprotein receptor targeting moiety.

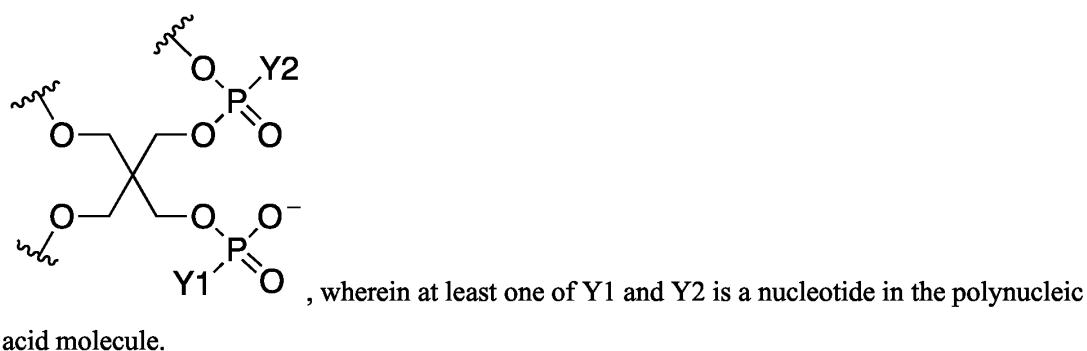
[0249] Embodiment 30. The polynucleic acid molecule conjugate of embodiment 29, wherein the asialoglycoprotein receptor targeting moiety comprises N-Acetylgalactosamine (GalNAc) or galactose.

[0250] Embodiment 31. The polynucleic acid molecule conjugate of any one of embodiments 29-30, wherein the polynucleic acid molecule and the asialoglycoprotein receptor targeting moiety is coupled via a linker.

[0251] Embodiment 32. The polynucleic acid molecule conjugate of embodiment 31, wherein the linker is a cleavable linker.

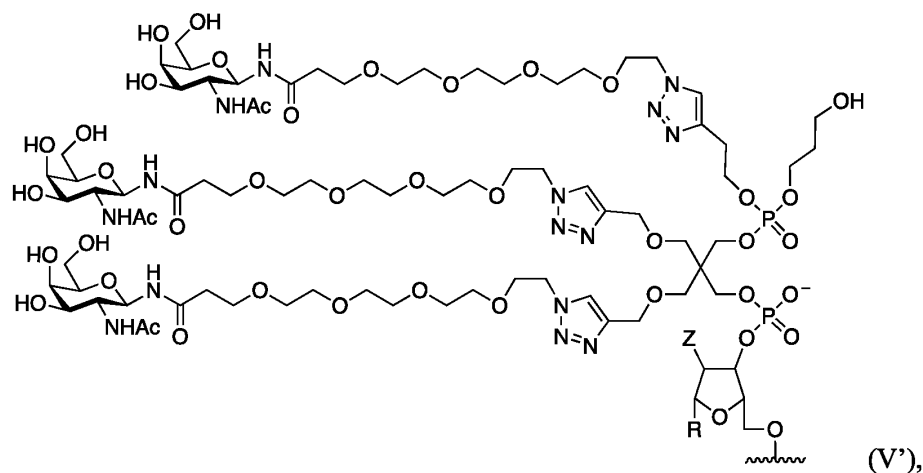
[0252] Embodiment 33. The polynucleic acid molecule conjugate of any one of embodiments 30-31, wherein the GalNAc comprises an anomeric carbon bonded to trivalent, tetravalent linker, pentavalent, or hexavalent linker, wherein the anomeric carbon is part of a hemiaminal group.

[0253] Embodiment 34. The polynucleic acid molecule conjugate of any one of embodiments 31-33, wherein the linker comprises formula (IV) below,

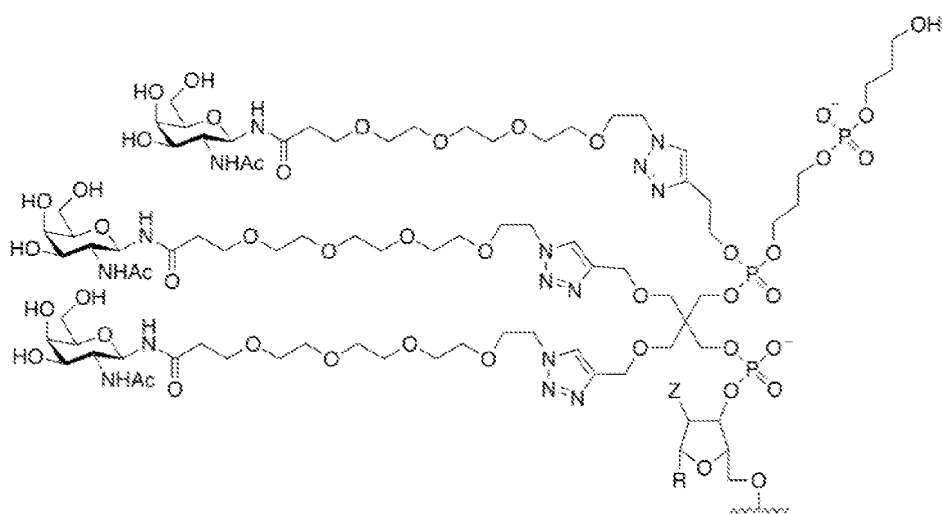


[0254] Embodiment 35. The polynucleic acid molecule conjugate of embodiment 34, wherein the Y1 is the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule.

[0255] Embodiment 36. The polynucleic acid molecule conjugate of any one of embodiments 31-35, wherein the linker and the asialoglycoprotein receptor targeting moiety with the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule are shown in Formula (V'), Formula (V'''), Formula (V'''), or Formula (V'''):

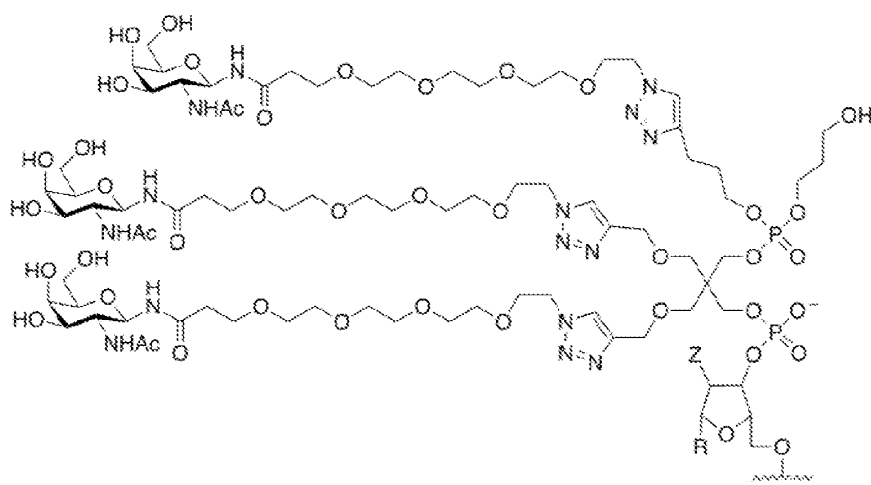


wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others;



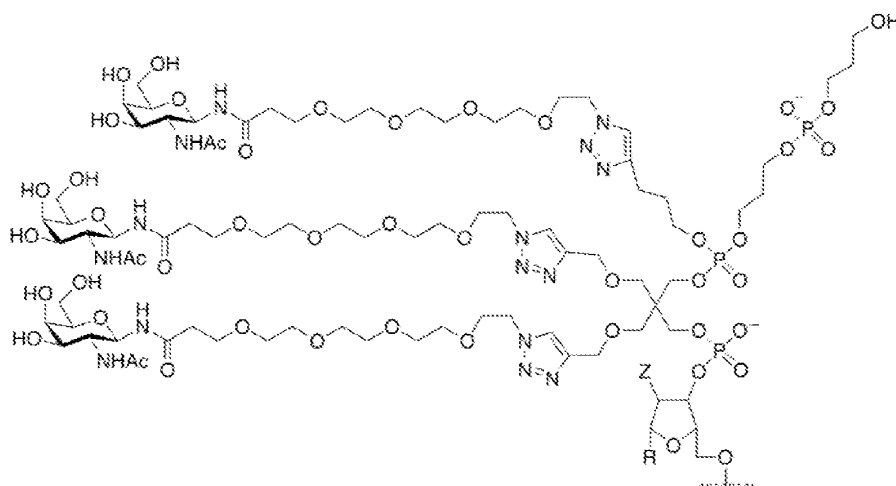
(V'''),

wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



(V'''''), wherein

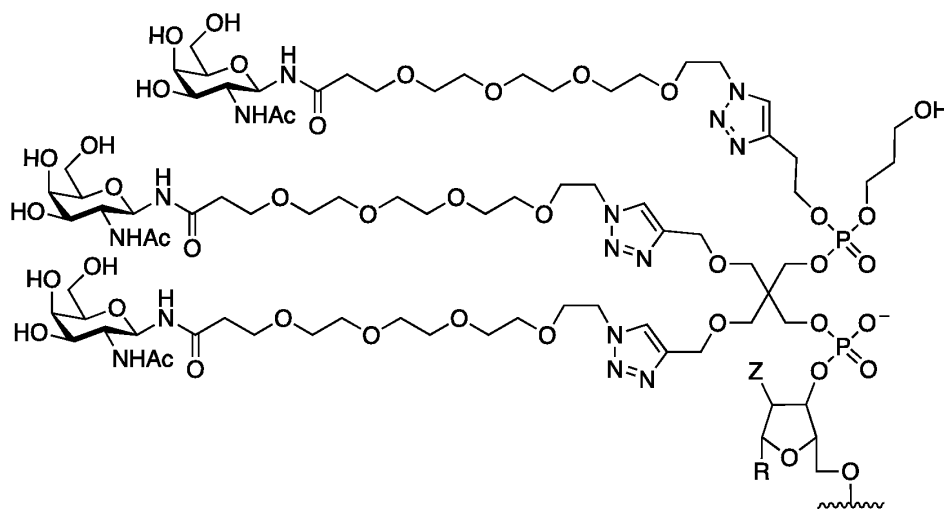
Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others; or



(V'''''), wherein

Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0256] Embodiment 37. The polynucleic acid molecule conjugate of embodiment 36, wherein the linker and the asialoglycoprotein receptor targeting moiety with the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule are shown in Formula (V'):



(V'), wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0257] Embodiment 38. A pharmaceutical composition comprising a polynucleic acid molecule of any one of embodiments [0220]-29Error! Reference source not found. or a polynucleic acid molecule conjugate of any one of embodiments 30-37, and a pharmaceutically acceptable excipient.

[0258] Embodiment 39. The pharmaceutical composition of embodiment 38, wherein the pharmaceutical composition is formulated as a nanoparticle formulation.

[0259] Embodiment 40. The pharmaceutical composition of embodiment 38 or embodiment 39, wherein the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.

[0260] Embodiment 41. A method of modulating expression of lipoprotein(a) (Lp(a)) gene in a subject in need thereof, comprising:

[0261] administering to the subject a polynucleic acid molecule of any one of embodiments [0220]-28, a polynucleic acid molecule conjugate of any one of embodiments 29-37, or a pharmaceutical composition of any one of embodiments 38-40, thereby modulating the expression of Lp(a) gene in the subject in need thereof.

[0262] Embodiment 42. A method for treating or preventing a cardiovascular disease or a lipid disorder, comprising

[0263] administering to the subject a polynucleic acid molecule of any one of embodiments [0220]-28, a polynucleic acid molecule conjugate of any one of embodiments 29-37, or a pharmaceutical composition of any one of embodiments 38-40, thereby modulating the expression of Lp(a) gene in the subject in need thereof.

[0264] Embodiment 43. The method of embodiment 41 or 42, wherein the polynucleic acid molecule is administered at a dose sufficient to decrease the expression of Lp(a) gene in a cell of said subject by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% compared to a control.

[0265] Embodiment 44. The method of embodiment 41 or 42, wherein the polynucleic acid molecule is administered at a dose sufficient to decrease plasma Lp(a) level of said subject by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% compared to a control.

[0266] Embodiment 45. The method of any one of embodiments 41-44, wherein the polynucleic acid molecule is administered in at least two doses comprising an initial dose and a secondary dose.

[0267] Embodiment 46. The method of embodiment 45, wherein the secondary dose is administered 1 to 30 days after the initial dose is administered.

[0268] Embodiment 47. The method of any one of embodiments 42-46, wherein the cardiovascular disease is coronary artery disease, acute myocardial infarction, asymptomatic carotid atherosclerosis, stroke, atrial fibrillation, or peripheral artery occlusive disease.

[0269] Embodiment 48. The method of any one of embodiments 42-46, wherein the lipid disorder is hyperlipidemia or hypercholesterolemia.

EXAMPLES

[0270] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1 – *In vitro* efficacy of siRNAs targeting Lp(a) in Primary Human Hepatocytes (PHH)

[0271] Primary human hepatocytes were thawed and plated on collagen-coated 96-well plates at a density of 9×10^4 cells per well. Hepatocytes were treated with conjugated siRNAs in the absence of transfection reagents (free uptake). Cells were treated with siRNAs with a concentrations at $10\mu\text{M}$ or $0.5\mu\text{M}$. Untreated PHHs were used as negative control. An siRNA targeting an unrelated gene (Ahsa1) was also used as a negative control. Cells were incubated at 37°C , 5% CO_2 for 48h. At the end of the incubation period, the cells were lysed, and the relative expression of the target gene was measured by branched DNA (bDNA) assay and normalized to a house-keeping gene using standard protocols.

[0272] The modifications of the sense and antisense strands of the siRNAs tested are listed in **Table 1**. Note that each of the sense strand sequences was coupled to a GalNAc-L96 at its 3' end. The *in vitro* potency data of the siRNAs is provided in **Table 3**.

[0273] Forty-eight (48) Lp(a) siRNAs were selected for dose response relationship according to standard dose response curve protocol. The doses tested include 10.0, 3.33, 1.11, 0.37, 0.12, 0.04, 0.01, 0.005, 0.002, and $0.001\mu\text{M}$ of the siRNA. The siRNAs were purified to at least approximately 85%.

[0274] A summary of the dose response curve data is provided in **Table 4**. The dose response curves are provided in **FIGs. 1A-1VV**.

Example 2 - Testing Lp(a) siRNAs in Non-human Primates

[0275] Fifteen (15) Lp(a) siRNAs (denoted as “SRS-000008” to “SRS-000022” from **Table 2**) were tested in a non-human primate study. For each siRNA, the 3' end of the passenger/sense strand was conjugated with a GalNAc via X2 (*see* Formula (V')). The Lp(a) siRNAs had sequences which were cross reactive with the cynomolgus monkey LPA gene. Male cynomolgus monkeys ($n=4$ per treatment group/siRNA) were administered a single 3 mg/kg subcutaneous injection of Lp(a) siRNA constructs SRS-000008 through SRS-000022. Animals were fasted overnight prior to collection of blood samples on day -1 (pre-dose) and on, days 3, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84. Lp(a) circulating protein levels in all serum samples were analyzed using an Lp(a) ELISA assay (Abcam, catalog # ab212165).

Formulation Preparation

[0276] Preparation of siRNAs was conducted on the dosing day under aseptic conditions at room temperature. The siRNAs were dissolved with sodium chloride and swirled or stirred until fully dissolved. The solution was filtered with a 0.22 μ M sterile filter and the solution was collected in a sterile container. The formulation was stored at 2-8°C. The siRNAs were dissolved by the appropriate amount of vehicle to get the concentration of 10mg/mL as the dosing formulations, respectively. On the day of dosing, siRNA formulations were stored at 2-8°C for dosing. The dosing procedure was finished within 6 hours.

Animals

[0277] Cynomolgus monkeys were used in the study. Animals were housed in a group of 5 or less of the same dose level in stainless steel cages, and in an environmentally monitored, well-ventilated room (Conventional grade) maintained at a temperature of 18°C-26°C and a relative humidity of 40%-70%. Fluorescent lighting provided illumination approximately 12 hours per day.

Experimental Design

[0278] To obtain groups that were comparable by body weight in the same sex, all monkeys were randomly assigned to respective treatment groups using a computer-generated randomization procedure. The body weights required for randomization were obtained on Day -5 (5 days prior to the first dosing). After randomization, monkeys were assigned to one of the treatment groups.

[0279] Each monkey in each group was given an siRNA formulation via subcutaneous injection with single or multipoint on skin of on the hindlimb and/or neck and back using a suitable disposable syringe and supporting needle. The hair around the injection site was shaved prior to dosing, and each injection point received no more than 2 mL. Doses were calculated based upon the most currently scheduled body weight.

[0280] Blood samples for lipoprotein A (Lp(a)) serum concentration detection were collected via forelimb or hindlimb subcutaneous vein. Monkeys were fasted overnight prior to blood collection for Lp(a) serum concentration evaluation.

[0281] Samples of whole blood were added into centrifuge tubes coated with separation gel and coagulator, and stored temporarily and transferred at room temperature. The blood samples were handled within 2 hours and centrifuged at 1500 g for 10 minutes at room temperature. After the centrifugation, the serum was aliquoted into 2 new tubes and transferred into newly labeled centrifuge tubes. All samples were stored equal to or below -20°C and avoided repeated freeze-thaws. Watson LIMS 7.5 system was used to manage the samples. ELISA kits (Catalog number: ab212165; Manufacturer: Abcam) were used for Lp(a) serum concentration analysis.

Data Analysis

Lp(a) serum concentrations were determined from serum samples collected on day -1 (pre-dose) and days 3, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84 using an ELISA assay (Abcam, catalog # ab212165). Results for each individual animal were expressed as the % change of circulating Lp(a) protein relative to the pre-dose (day -1) timepoint. The mean % change for each treatment group along with standard deviation was presented in **Table 6** and plotted in **FIG. 2**.

Example 3 - Testing Lp(a) siRNAs in Non-human Primates

[0282] In a similar study described in example 2, four Lp(a) siRNAs, SRS-000013, SRS-000016, SRS-000017, and SRS-000018 were tested in cynomolgus monkeys. For each siRNA, the 3' end of the passenger/sense strand was conjugated with a GalNAc via X2 (*see* Formula (V')). The Lp(a) siRNAs had sequences which were cross reactive with the cynomolgus monkey LPA gene. Male cynomolgus monkeys (n=4 per treatment group/siRNA) were administered a single 1 mg/kg subcutaneous injection of each Lp(a) siRNA. Animals were fasted overnight prior to collection of blood samples on day -1 (pre-dose) and on days 3, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 85. Additional blood samples were collected on days 98, 105, 112, 119, 126, 133, and 140 for SRS-000016 and SRS-000018 treated groups. Lp(a) circulating protein levels in all serum samples were analyzed using an Lp(a) ELISA assay (Abcam, catalog # ab212165). Results for each individual animal were expressed as the % change of circulating Lp(a) protein relative to the pre-dose (day -1) timepoint. The mean % change for each treatment group along with standard deviation was presented in **Table 7** and plotted in **FIG. 3**.

[0283] While preferred aspects of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such aspects are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the aspects of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby

Table 2.

Compd	sIRNA ID	Unmodified Antisense Sequence (5'→3')	SEQ ID NO	Modified Antisense Sequence (5'→3')	SEQ ID NO	sIRNA ID	Unmodified Sense Sequence (5'→3')	SEQ ID NO	Modified Sense Sequence (5'→3')	SEQ ID NO	Position at Human Transcript
SRS-000008	G-000008	UAGAU GACCAAGCUUGGCAG	4	usAfsagauAfccaaGfeUfuGficcagg susC	158	P-000008	CCUGCCAAGCUUGGUCAUC UA	312	cscsucccAfAcGfcUfgugcaucua	466	204
SRS-000009	G-000009	UAUAGAUGACCAAGCUUGGCAGG	5	usAfsuagaUfigaccAfAcGfcUfuggccas gsg	159	P-000009	UGCCAAGCUUGGUCAUCU AUA	313	ugscccaaGfcUfuOfigucaucu aaa	467	206
SRS-000010	G-000010	UCAUAGAUGACCAAGCUUGGCAG	6	usCfsauagAfugacCfaAfGcfUfuggcs asg	160	P-000010	GCCAAGCUUGGUCAUCUA UGA	314	gscscaagCftuUfgGfuccaucua uga	468	207
SRS-000011	G-000011	UCGACGGCAGUCCCCUUCUGC	11	usCfsicagcGfrcaguCfcCftuUfuccgcs usc	165	P-000011	CGCAGAAAGGACUGCCGUC GA	319	csgscagaAfIgGfGfAfcugccogu cga	473	382
SRS-000012	G-000012	UUUAGGCUUGGAACCGGGG	18	usUfiscuagOfrcungGfAcCfcGfigggu sasa	172	P-000012	ACCCCUGUCCAAAGCCUAG AA	326	ascsccccGfuUfcCfaagccua gaa	480	416
SRS-000013	G-000013	UAGCCUCUAGGCUUGGAACC	21	usAfsagcuCfuuagCftuUfgGfAACgs gsg	175	P-000013	CGGUUCCAAAGCCUAGAGGC UA	329	csgsgnuuCfAcAfGcfCfuaaggg cua	483	420
SRS-000014	G-000014	UUUACCGUGUAGCACUCCU	44	usUfisuaceCfugguAfGcfCfAccug ssca	198	P-000014	CAGGAGUGCTUACCACCGGU AAA	352	csasggagUfGcfCftuAfccaggu aaa	506	1163
SRS-000015	G-000015	UUGUCCAUUACCGGUGUAGC	47	usUfisuageAfnuacCfIgUfgGfuaaca scsu	201	P-000015	UGCUACCAACGGUAAUUGGA CAA	355	usgsuacuCfAcCfGcfGfuaaugga caa	509	1169
SRS-000016	G-000016	UCUCUGUCCAUUACCGUGGU	49	usCfsicuagUfrcanUfAcCfcGfugguas gsc	203	P-000016	UACCAAGGUAAUGGACAG AGA	357	usasccacGfGfUfAcUfuggagag aga	511	1172
SRS-000017	G-000017	UAUTUGUCAGGUUGCAGUA	60	usAfsunuguFhuagGfuUfgCfaguac susC	214	P-000017	GUACUGCAACCUUGACACAA UA	368	gsauscuugCfAcAfCcFugacaca aaa	522	2749
SRS-000018	G-000018	UUGGUCUCAGCAUUGUGUC	64	usUfissgucCfuggagCftuUfuGfuga sgsg	218	P-000018	UGACACAUAUGCUCAGACGC AA	372	usgsacacAfAuUfgCfucagagc caa	526	2760
SRS-000019	G-000019	UUAAACUCUGUCCAUAAUGGU	88	usUfisaacuCfugucCfAuUfAfugguas gsu	242	P-000019	UACCAUUUUGGACACAGAGU UAA	396	uasascrauUfAuUfgGfAcagagu uaa	550	3227
SRS-000020	G-000020	UCCAAGCUUGGCAAGUUCUU	89	usCfsicaagCfuinggCfAcAfGufucmucs csu	243	P-000020	GAAGAACUUGGCCAAGCUU GGA	397	gsasagaaCftuUfgCfCaagcu gga	551	3276
SRS-000021	G-000021	UAGAU GACCAAGCUUGGCAG	90	usAfsagauAfccaaGfeUfuGficcags usu	244	P-000021	CUUGCCAAGCUUGGUCAUC UAC	398	csusugccAfAcGfcUfuggcaucua cua	552	3282
SRS-000022	G-000022	UGUCCGACUAUUGCUGUGU	98	usGfisguceGfAcuaUfGcfCtuGfugug sgsu	252	P-000022	CACACCAACGAUAGUCGGAC CA	406	csasaccAfGcfCfAuUfagucga cca	560	3309

As used herein, "A" refers to adenosine-3'-phosphate; "a" refers to 2'-fluoro-adenosine-3'-phosphate; "A^F" refers to 2'-fluoroadenosine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methyl-guanosine-3'-phosphate; "G^F" refers to 2'-O-methyl-guanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyl-uridine-3'-phosphate; "U^F" refers to 2'-fluoro-uridine-3'-phosphate; "U^M" refers to 5-methyl-uridine-3'-phosphate; "C" refers to cytosine-3'-phosphate; "c" refers to 2'-O-methyl-cytosine-3'-phosphate; "T" refers to thymine-3'-phosphate; "t" refers to 2'-fluoro-thymine-3'-phosphate; "T^F" refers to 5-methyl-thymine-3'-phosphate; "I" refers to 2'-fluoro-5-methyl-uridine-3'-phosphate; "s" refers to 3'-phosphothioate. The "position at human transcript" is defined as the 5' position of a 21-mer target site in human transcript (NCBI Reference Sequence No: NM_005577.4). Each modified sense sequence is coupled to a targeting moiety (e.g., GalNAc or galactose) at its 3' end via a linker (e.g., Formula V', Y'''''', Y'''''''', or Y''''''').

Table 3. siRNA efficacy in primary human hepatocytes (PHH)

Compd ID	10 μ M		0.5 μ M		Position of 21mer Sense Strand
	MV quadruplicates [% residual target mRNA]	SD quadruplicates	MV quadruplicates [% residual target mRNA]	SD quadruplicates	
Untreated	118	8	94	10	n/a
SRS-000023	98	10	87	3	198
SRS-000024	85	11	79	4	199
SRS-000025	100	2	83	6	202
SRS-000026	73	6	63	5	204
SRS-000027	82	14	85	1	206
SRS-000028	66	11	68	4	207
SRS-000029	78	6	70	3	260
SRS-000030	97	9	83	6	374
SRS-000031	107	10	91	6	379
SRS-000032	100	9	80	10	381
Untreated	102	10	94	6	n/a
Control (Ahsa1)	96	15	86	6	n/a
SRS-000033	82	13	79	6	382
SRS-000034	96	17	79	3	383
SRS-000035	94	12	76	3	406
SRS-000036	92	6	92	11	407
SRS-000037	94	5	81	7	408
SRS-000038	93	2	82	6	411
SRS-000039	87	3	74	4	412
SRS-000040	73	11	75	1	416
SRS-000041	91	9	86	5	417
SRS-000042	93	8	85	2	419
untreated	96	3	90	5	n/a
untreated	100	9	102	2	n/a
SRS-000043	69	5	80	3	420
SRS-000044	81	6	89	3	421
SRS-000045	82	11	87	6	425
SRS-000046	86	9	97	7	427
SRS-000047	83	11	91	10	430
SRS-000048	95	14	99	6	435
SRS-000049	90	3	80	27	436
SRS-000050	70	31	97	4	438
SRS-000051	88	9	94	10	439
SRS-000052	85	5	94	8	442
untreated	96	8	96	6	n/a
Control (Ahsa1)	105	1	117	5	n/a
SRS-000053	97	8	98	2	446
SRS-000054	67	4	89	1	470
SRS-000055	82	3	94	5	471
SRS-000056	77	6	87	3	493
SRS-000057	69	8	82	4	494
SRS-000058	63	7	73	3	503
SRS-000059	100	5	99	8	504
SRS-000060	100	6	103	8	505
SRS-000061	99	8	98	2	515
SRS-000062	86	4	89	3	541
untreated	100	3	85	8	n/a
untreated	89	7	102	3	n/a
SRS-000063	80	6	92	5	544

SRS-000064	63	10	69	4	546
SRS-000065	71	4	89	9	1162
SRS-000066	66	4	83	3	1163
SRS-000067	65	4	96	31	1165
SRS-000068	87	5	93	5	1168
SRS-000069	67	3	82	11	1169
SRS-000070	92	6	91	5	1171
SRS-000071	69	3	79	6	1172
SRS-000072	86	3	89	5	1174
untreated	93	11	100	7	n/a
Control (Ahsa1)	94	7	118	14	n/a
SRS-000073	66	1	76	5	1177
SRS-000074	62	2	77	5	1178
SRS-000075	76	2	89	6	2684
SRS-000076	83	2	98	4	2698
SRS-000077	87	5	102	5	2701
SRS-000078	78	9	89	6	2705
SRS-000079	81	2	92	34	2706
SRS-000080	90	8	99	11	2707
SRS-000081	90	3	91	9	2747
SRS-000082	70	4	82	8	2749
untreated	95	2	91	7	n/a
untreated	101	7	109	11	n/a
SRS-000083	89	4	95	10	2751
SRS-000084	84	19	98	9	2753
SRS-000085	85	6	102	8	2754
SRS-000086	78	2	78	7	2760
SRS-000089	81	7	90	7	2815
SRS-000090	85	6	92	5	2823
SRS-000091	83	6	88	5	2841
SRS-000092	96	3	101	3	2843
SRS-000093	80	7	76	4	2894
SRS-000094	91	6	96	1	3023
untreated	101	7	96	4	n/a
Control (Ahsa1)	108	5	94	7	n/a
SRS-000095	86	4	78	3	3044
SRS-000096	92	8	86	4	3047
SRS-000097	87	7	91	9	3049
SRS-000098	92	7	86	5	3050
SRS-000099	90	3	92	7	3090
SRS-000100	92	4	93	5	3094
SRS-000101	97	8	93	7	3095
SRS-000102	92	5	93	4	3096
SRS-000103	99	6	100	7	3098
SRS-000104	97	7	106	3	3158
untreated	90	20	101	9	n/a
untreated	97	10	144	64	n/a
SRS-000105	83	5	88	7	3218
SRS-000106	79	5	84	15	3219
SRS-000107	82	7	77	5	3220
SRS-000108	82	8	78	6	3223
SRS-000109	83	7	79	10	3226
SRS-000110	66	7	73	18	3227
SRS-000111	70	5	71	8	3276
SRS-000112	56	7	56	13	3282
SRS-000113	56	1	60	2	3284
SRS-000114	48	3	57	3	3285

untreated	91	9	77	2	n/a
Control (Ahsal)	108	5	95	1	n/a
SRS-000115	97	6	82	6	3303
SRS-000116	93	9	89	10	3304
SRS-000117	89	7	83	9	3305
SRS-000118	91	5	77	7	3307
SRS-000119	89	4	75	4	3308
SRS-000120	79	4	77	4	3309
SRS-000121	95	5	79	6	3316
SRS-000122	94	9	84	5	3317
SRS-000123	91	10	78	2	3320
SRS-000124	97	13	82	10	3396
untreated	104	13	83	6	n/a
untreated	99	6	99	3	n/a
SRS-000125	96	7	91	5	3397
SRS-000126	93	11	90	7	3398
SRS-000127	91	12	87	4	3399
SRS-000128	93	10	86	5	3406
SRS-000129	91	7	90	2	3407
SRS-000130	91	9	88	7	3464
SRS-000131	88	12	92	6	3735
SRS-000132	91	13	85	5	3737
SRS-000133	77	2	84	5	3738
SRS-000134	85	10	81	3	3741
untreated	97	7	89	5	n/a
Control (Ahsal)	108	4	105	5	n/a
SRS-000135	94	4	89	11	3778
SRS-000136	90	2	94	9	3779
SRS-000137	89	3	90	5	3780
SRS-000138	88	5	86	5	3783
SRS-000139	94	9	86	4	3790
SRS-000140	80	6	82	6	3991
SRS-000141	90	4	91	5	4049
SRS-000142	92	2	83	9	4053
SRS-000143	96	2	75	17	4055
SRS-000144	94	11	85	12	4056
untreated	96	9	95	10	n/a
untreated	101	3	94	3	n/a
SRS-000145	99	9	90	9	4066
SRS-000146	91	12	78	5	4067
SRS-000147	93	7	75	4	4138
SRS-000148	91	14	80	3	4139
SRS-000149	95	12	80	4	4150
SRS-000150	93	14	70	5	4450
SRS-000151	96	12	74	3	4645
SRS-000152	97	9	73	4	4646
SRS-000153	100	12	73	2	4733
SRS-000154	104	10	70	2	4802
untreated	103	5	77	3	n/a
Control (Ahsal)	97	6	110	17	n/a
SRS-000155	81	15	83	8	4803
SRS-000156	83	2	110	42	4805
SRS-000157	84	5	82	10	4806
SRS-000158	87	2	76	5	4808
SRS-000159	83	3	75	6	4812
SRS-000160	84	7	79	7	4823

SRS-000161	89	3	75	10	4926
SRS-000162	89	2	80	10	4969
SRS-000163	90	4	84	14	4970
SRS-000164	97	14	86	14	5073
untreated	99	8	96	12	n/a
untreated	121	18	102	7	n/a
SRS-000165	106	5	98	2	5121
SRS-000166	101	9	92	4	5122
SRS-000167	96	9	92	6	5123
SRS-000168	82	1	78	10	5124
SRS-000169	104	7	91	7	5126
SRS-000170	95	10	81	13	5127
SRS-000171	100	10	92	8	5128
SRS-000172	96	6	86	11	5129
SRS-000173	92	8	79	5	5130
SRS-000174	100	5	87	8	5132
untreated	101	5	84	10	n/a
Control (Ahsa1)	92	14	117	11	n/a
SRS-000175	75	8	81	10	5505
SRS-000176	76	6	92	7	5866
SRS-000087	85	5	88	3	2762
SRS-000088	81	3	90	3	2764
untreated	86	8	97	4	n/a

MV: mean value. SD: standard deviation. The “position of 21mer sense strand” is defined as the 5' position of a 21-mer sense strand target site in human transcript (NCBI Reference Sequence No: NM_005577.4)

Table 4. Dose Response Curve in Primary Human Hepatocyte

Compd ID	Transcript Start Site (5' pos of 21mer Sense Strand)	dose [μM]	MV quadruplicates [% residual target mRNA]	SD quadruplicates
SRS-000026	204	Mock	99	8
		10.0	40	8
		3.33	44	4
		1.11	56	3
		0.37	63	9
		0.12	65	3
		0.04	68	7
		0.01	75	3
		0.005	73	2
		0.002	79	4
0.001	86	4		
Control (Ahsa1)		1.11 μM	95	2
		Mock	101	9
SRS-000027	206	10.0	51	4
		3.33	54	4
		1.11	59	7
		0.37	70	7
		0.12	79	6
		0.04	88	4
		0.01	93	9
		0.005	92	3
		0.002	95	13
		0.001	102	10
		Mock	105	15

		Mock	97	5
SRS-000028	207	10.0	51	2
		3.33	55	4
		1.11	63	9
		0.37	58	5
		0.12	68	5
		0.04	94	3
		0.01	90	8
		0.005	83	5
		0.002	94	9
		0.001	93	4
Control (Ahsa1)		1.11 μ M	99	6
		Mock	105	2
SRS-000029	260	10.0	59	7
		3.33	60	4
		1.11	75	11
		0.37	70	4
		0.12	75	2
		0.04	82	4
		0.01	86	6
		0.005	82	5
		0.002	88	3
		0.001	87	4
		Mock	100	10
		Mock	98	11
SRS-000033	382	10.0	89	11
		3.33	82	4
		1.11	90	9
		0.37	92	7
		0.12	88	12
		0.04	91	10
		0.01	97	6
		0.005	97	9
		0.002	90	11
		0.001	97	5
Control (Ahsa1)		1.11 μ M	99	9
		Mock	102	3
SRS-000040	416	10.0	78	7
		3.33	81	6
		1.11	87	4
		0.37	87	3
		0.12	90	5
		0.04	111	23
		0.01	99	2
		0.005	100	7
		0.002	96	13
		0.001	102	6
		Mock	101	6
		Mock	100	4
SRS-000043	420	10.0	75	6
		3.33	74	2
		1.11	76	3
		0.37	83	5
		0.12	78	4
		0.04	87	9
		0.01	89	5
		0.005	88	5
		0.002	94	7

		0.001	92	3
Control (Ahsa1)		1.11 μM	102	5
		Mock	100	5
SRS-000044	421	10.0	73	4
		3.33	74	2
		1.11	84	5
		0.37	83	7
		0.12	79	4
		0.04	82	7
		0.01	81	3
		0.005	88	8
		0.002	93	4
		0.001	93	3
		Mock	99	6
		Mock	89	8
SRS-000045	425	10.0	74	8
		3.33	74	8
		1.11	79	9
		0.37	81	13
		0.12	80	12
		0.04	85	18
		0.01	87	6
		0.005	85	10
		0.002	97	10
		0.001	87	6
Control (Ahsa1)		1.11 μM	99	6
		Mock	106	19
SRS-000050	438	10.0	84	10
		3.33	84	6
		1.11	93	7
		0.37	86	7
		0.12	93	8
		0.04	89	7
		0.01	101	11
		0.005	95	3
		0.002	105	2
		0.001	101	9
		Mock	107	8
		Mock	101	5
SRS-000054	470	10.0	61	4
		3.33	64	6
		1.11	73	4
		0.37	78	5
		0.12	80	4
		0.04	88	5
		0.01	90	7
		0.005	88	4
		0.002	95	10
		0.001	90	8
Control (Ahsa1)		1.11 μM	102	11
		Mock	95	7
SRS-000056	493	10.0	57	3
		3.33	60	2
		1.11	73	7
		0.37	76	6
		0.12	78	7
		0.04	85	4
		0.01	94	10
		0.005	92	8

		0.002	98	8
		0.001	99	13
		Mock	102	4
		Mock	102	7
SRS-000057	494	10.0	58	2
		3.33	56	2
		1.11	64	5
		0.37	71	7
		0.12	75	8
		0.04	87	7
		0.01	91	8
		0.005	89	2
		0.002	98	2
		0.001	101	5
Control (Ahsa1)		1.11 μM	101	3
		Mock	98	4
SRS-000058	503	10.0	71	2
		3.33	73	6
		1.11	67	9
		0.37	71	7
		0.12	67	6
		0.04	69	3
		0.01	73	5
		0.005	74	3
		0.002	79	7
		0.001	85	13
		Mock	98	10
		Mock	107	6
SRS-000064	546	10.0	46	2
		3.33	50	2
		1.11	58	3
		0.37	63	4
		0.12	69	5
		0.04	72	2
		0.01	77	2
		0.005	74	4
		0.002	82	2
		0.001	90	2
Control (Ahsa1)		1.11 μM	92	6
		Mock	108	4
SRS-000065	1162	10.0	99	14
		3.33	76	2
		1.11	104	4
		0.37	100	4
		0.12	104	8
		0.04	97	8
		0.01	96	10
		0.005	99	8
		0.002	103	8
		0.001	102	6
		Mock	93	6
		Mock	101	10
SRS-000066	1163	10.0	71	4
		3.33	72	5
		1.11	86	9
		0.37	81	8
		0.12	92	9
		0.04	96	11
		0.01	95	7

		0.005	89	8
		0.002	91	6
		0.001	94	7
	Control (Ahsal)	1.11 μ M	97	3
SRS-000067	1165	10.0	81	5
		3.33	79	8
		1.11	95	5
		0.37	88	8
		0.12	97	6
		0.04	93	4
		0.01	102	9
		0.005	92	7
		0.002	103	5
		0.001	101	7
		Mock	98	4
		Mock	106	1
SRS-000069	1169	10.0	81	1
		3.33	77	2
		1.11	80	5
		0.37	82	4
		0.12	81	4
		0.04	84	8
		0.01	85	4
		0.005	81	3
		0.002	87	3
		0.001	88	3
	Control (Ahsal)	1.11 μ M	93	5
		Mock	102	6
SRS-000071	1172	10.0	87	9
		3.33	85	3
		1.11	92	9
		0.37	87	4
		0.12	92	5
		0.04	93	6
		0.01	85	4
		0.005	93	5
		0.002	87	7
		0.001	93	4
		Mock	98	5
		Mock	99	12
SRS-000073	1177	10.0	55	5
		3.33	58	3
		1.11	71	4
		0.37	75	3
		0.12	76	3
		0.04	80	5
		0.01	80	6
		0.005	84	7
		0.002	96	6
		0.001	100	9
	Control (Ahsal)	1.11 μ M	100	8
		Mock	104	7
SRS-000074	1178	10.0	49	2
		3.33	55	3
		1.11	62	8
		0.37	70	2
		0.12	74	2
		0.04	81	2
		0.01	88	9

		0.005	88	5
		0.002	98	9
		0.001	102	3
		Mock	97	3
		Mock	96	8
SRS-000075	2684	10.0	84	9
		3.33	87	8
		1.11	96	11
		0.37	93	6
		0.12	98	9
		0.04	93	5
		0.01	96	4
		0.005	96	3
		0.002	96	5
		0.001	95	3
Control (Ahsa1)		1.11 μM	98	3
		Mock	111	2
SRS-000078	2705	10.0	88	1
		3.33	89	8
		1.11	96	4
		0.37	92	4
		0.12	107	11
		0.04	107	16
		0.01	86	4
		0.005	91	11
		0.002	94	3
0.001	96	3		
		Mock	95	8
		Mock	88	6
SRS-000079	2706	10.0	58	1
		3.33	57	2
		1.11	59	5
		0.37	64	3
		0.12	64	3
		0.04	73	7
		0.01	67	6
		0.005	68	3
		0.002	75	4
0.001	80	5		
Control (Ahsa1)		1.11 μM	88	13
		Mock	125	12
SRS-000082	2749	10.0	77	13
		3.33	71	11
		1.11	80	13
		0.37	77	14
		0.12	77	10
		0.04	80	9
		0.01	87	14
		0.005	80	10
		0.002	85	14
0.001	94	8		
		Mock	100	14
		Mock	90	21
SRS-000086	2760	10.0	71	16
		3.33	56	6
		1.11	69	12
		0.37	60	5
		0.12	56	5
		0.04	57	3

		0.01	58	7
		0.005	58	6
		0.002	61	3
		0.001	72	3
Control (Ahsa1)		1.11 μ M	109	27
		Mock	99	4
SRS-000093	2894	10.0	61	4
		3.33	57	5
		1.11	60	9
		0.37	67	2
		0.12	75	2
		0.04	73	5
		0.01	75	9
		0.005	77	3
		0.002	84	4
		0.001	81	9
		Mock	103	10
		Mock	98	4
SRS-000106	3219	10.0	87	9
		3.33	90	19
		1.11	102	11
		0.37	87	7
		0.12	83	9
		0.04	84	9
		0.01	92	12
		0.005	79	13
		0.002	82	7
		0.001	85	6
Control (Ahsa1)		1.11 μ M	100	9
		Mock	99	19
SRS-000107	3220	10.0	85	5
		3.33	97	5
		1.11	100	9
		0.37	94	4
		0.12	93	7
		0.04	91	5
		0.01	94	8
		0.005	88	11
		0.002	95	12
		0.001	96	13
		Mock	103	6
		Mock	88	15
SRS-000108	3223	10.0	83	11
		3.33	84	6
		1.11	84	5
		0.37	55	20
		0.12	73	4
		0.04	67	6
		0.01	84	8
		0.005	68	11
		0.002	82	6
		0.001	100	8
Control (Ahsa1)		1.11 μ M	95	8
		Mock	109	2
SRS-000109	3226	10.0	94	7
		3.33	86	17
		1.11	83	14
		0.37	92	16
		0.12	80	9

		0.04	80	11
		0.01	81	15
		0.005	74	17
		0.002	84	6
		0.001	91	6
		Mock	108	9
		Mock	92	8
SRS-000110	3227	10.0	66	4
		3.33	62	3
		1.11	67	1
		0.37	58	11
		0.12	68	3
		0.04	79	6
		0.01	84	9
		0.005	82	11
		0.002	88	7
		0.001	94	4
Control (Ahsa1)		1.11 μM	101	4
		Mock	107	9
SRS-000111	3276	10.0	83	3
		3.33	82	2
		1.11	90	6
		0.37	85	2
		0.12	79	3
		0.04	82	3
		0.01	87	5
		0.005	84	7
		0.002	93	8
		0.001	96	4
		Mock	100	8
		Mock	92	4
SRS-000112	3282	10.0	48	5
		3.33	53	9
		1.11	52	4
		0.37	53	7
		0.12	54	3
		0.04	58	5
		0.01	68	6
		0.005	66	4
		0.002	75	4
		0.001	82	5
Control (Ahsa1)		1.11 μM	100	3
		Mock	91	5
SRS-000113	3284	10.0	55	6
		3.33	63	4
		1.11	84	7
		0.37	79	1
		0.12	76	3
		0.04	81	2
		0.01	87	4
		0.005	85	6
		0.002	88	7
		0.001	93	4
		Mock	95	5
		Mock	93	6
SRS-000114	3285	10.0	41	2
		3.33	42	2
		1.11	47	5
		0.37	60	3

		0.12	67	5
		0.04	74	2
		0.01	85	6
		0.005	75	6
		0.002	88	5
		0.001	92	8
Control (Ahsa1)		1.11 μM	99	6
		Mock	107	10
SRS-000120	3309	10.0	90	7
		3.33	87	7
		1.11	88	7
		0.37	93	6
		0.12	87	9
		0.04	94	5
		0.01	97	7
		0.005	86	2
		0.002	96	10
0.001	93	5		
		Mock	77	52
		Mock	94	8
SRS-000133	3738	10.0	82	5
		3.33	71	4
		1.11	83	4
		0.37	84	9
		0.12	87	4
		0.04	86	0
		0.01	91	9
		0.005	86	6
		0.002	95	5
0.001	102	3		
Control (Ahsa1)		1.11 μM	106	10
		Mock	103	5
SRS-000134	3741	10.0	97	2
		3.33	95	6
		1.11	103	8
		0.37	98	7
		0.12	102	5
		0.04	100	8
		0.01	105	11
		0.005	103	12
		0.002	104	17
0.001	111	6		
		Mock	97	14
		Mock	103	4
SRS-000135	3778	10.0	90	9
		3.33	87	10
		1.11	91	7
		0.37	106	23
		0.12	93	5
		0.04	89	4
		0.01	85	24
		0.005	91	5
		0.002	97	6
0.001	95	6		
Control (Ahsa1)		1.11 μM	94	4
		Mock	105	12
SRS-000140	3991	10.0	81	8
		3.33	77	3
		1.11	87	11

		0.37	85	8
		0.12	87	5
		0.04	90	4
		0.01	105	14
		0.005	93	1
		0.002	100	5
		0.001	99	4
		Mock	98	3
		Mock	114	17
SRS-000155	4803	10.0	77	12
		3.33	77	4
		1.11	86	8
		0.37	83	4
		0.12	78	3
		0.04	80	8
		0.01	84	2
		0.005	85	8
		0.002	89	1
		0.001	91	4
Control (Ahsa1)		1.11 μM	90	2
		Mock	104	6
SRS-000168	5124	10.0	65	3
		3.33	63	4
		1.11	82	17
		0.37	74	5
		0.12	72	8
		0.04	74	8
		0.01	86	8
		0.005	83	3
		0.002	88	9
		0.001	90	4
		Mock	92	8
		Mock	97	4
SRS-000175	5505	10.0	85	6
		3.33	88	7
		1.11	85	11
		0.37	82	7
		0.12	81	10
		0.04	87	14
		0.01	91	7
		0.005	88	8
		0.002	89	7
		0.001	92	4
Control (Ahsa1)		1.11 μM	102	4
		Mock	96	14
SRS-000176	5866	10.0	96	4
		3.33	95	5
		1.11	101	8
		0.37	93	18
		0.12	96	4
		0.04	96	5
		0.01	103	4
		0.005	99	3
		0.002	100	3
		0.001	101	6
		Mock	106	9
		Mock	92	7
SRS-000087	2762	10.0	89	6
		3.33	77	4

		1.11	96	18
		0.37	81	3
		0.12	76	6
		0.04	69	4
		0.01	83	13
		0.005	72	5
		0.002	79	7
		0.001	86	3
Control (Ahsa1)		1.11 μ M	94	4
		Mock	108	15
SRS-000088	2764	10.0	94	8
		3.33	86	13
		1.11	99	8
		0.37	95	7
		0.12	95	17
		0.04	99	14
		0.01	105	7
		0.005	97	12
		0.002	99	15
		0.001	97	10
		Control	106	6
MV: mean value. SD: standard deviation. The “Transcript Start Site” is defined as the 5’ position of a 21-mer sense strand target site in human transcript (NCBI Reference Sequence No: NM_005577.4)				

Table 5. Final dose responses in primary human hepatocyte

Compd ID	sRNA ID	Modified Antisense Sequence (5'→3')	SEQ ID NO.	sRNA ID	Modified Sense Sequence (5'→3')	SRQ ID NO.	IC50 (μM)	IC80 (μM)	Transcript Start Site in NM_005577.4	MV max KD at highest dose	SD max KD
SRS-000026	G-000008	usAfsaugAftcaAGfcUfuGfagcaggsg	158	P-000026	cscagccAfaGfcUfuggaucua	466	2.046722	127.9168	204	60.20508	7.820476
SRS-000027	G-000009	usAfsuagaUfagaccAfaGfcUfugccasgsg	159	P-000027	usgsccaaGfcUfuGfugcaucuaa	467	12.28532	#N/A	206	48.55853	3.722845
SRS-000028	G-000010	usCfsauagAfuagacCfaAfgCfuugccasag	160	P-000028	gsccsaagCfuUfgCfugcaucuauga	468	13.86981	#N/A	207	48.81948	2.262899
SRS-000029	G-000026	usAfsucaaGfccaGfcUfuUfuggguasgsu	161	P-000029	usascccaAfaUfgCfugggcuugaua	469	49.46417	4399.698	260	41.22481	7.184138
SRS-000033	G-000011	usCfsgacGfcaGfcUfuUfugcgsgusc	165	P-000033	csgscagaAfgGfgAfcugcguega	473	#N/A	#N/A	382	10.80257	10.65991
SRS-000040	G-000012	usUfscuagGfcaGfcUfuUfugggusasa	172	P-000040	ascscggGfuUfcCfaagccuagaa	480	#N/A	#N/A	416	22.43361	6.593784
SRS-000043	G-000013	usAfsagcuCfuagGfcUfuUfgfcaaccgsag	175	P-000043	csgsguucCfaAfgCfuaagagcuca	483	#N/A	#N/A	420	25.05174	6.339611
SRS-000044	G-000038	usGfsagccUfcuagGfcUfuGfgaaccsgsg	176	P-000044	gsgsuuccAfaGfcCfuagagcuca	484	#N/A	#N/A	421	27.05507	3.55983
SRS-000045	G-000039	usGfsaaggAfgccuCfuAfgGfcaunggsasa	177	P-000045	cscsaagCfuAfgAfggcuucuca	485	#N/A	#N/A	425	25.79898	7.67276
SRS-000050	G-000044	usCfsggugCfuugUfcGfgAfgaggscsc	182	P-000050	csusccuUfcGfaAftcaagcaacca	490	#N/A	#N/A	438	16.28757	9.523407
SRS-000054	G-000048	usUfsagcaCfuccuGfcAftcCfcaagsgsc	186	P-000054	cscsugggGfuGfcAfgagugcuua	494	39.77935	1302.725	470	38.88559	3.700684
SRS-000056	G-000050	usGfsauaaCfuugUfcCfaUfuaccasug	188	P-000056	usgsuuaUfgCfaCfagaguuauca	496	61.08738	#N/A	493	43.48794	2.714998
SRS-000057	G-000051	usCfsgauaAfcuUfcUfuGfuaaccasau	189	P-000057	gsgsuauGfgAftcAfgaguuauca	497	#N/A	#N/A	494	41.58673	1.838853
SRS-000058	G-000052	usUfsaugUfcaGfcUfuAftcuugsgusc	190	P-000058	csasagaguUfaUfcCfagggcacaaua	498	#N/A	#N/A	503	28.61084	2.377041
SRS-000064	G-000058	usAfsaugAftcaAGfcUfuGfagcaggsgsu	196	P-000064	cscagccAfaGfcUfuggaucua	504	4.327232	961.917	546	54.44387	2.479078
SRS-000065	G-000059	usUfsaccUfgguAftcAftcUfcuagcsasc	197	P-000065	gsccsagaGfuGfcUfaccagguua	505	#N/A	#N/A	1162	1.002411	13.93118
SRS-000066	G-000014	usUfsuaccGfuugUfgCfaCfuuccgsca	198	P-000066	csasggagUfgCfuAftccaggguaa	506	123.3882	1424.798	1163	29.36707	4.073732
SRS-000067	G-000060	usCfsauuaCfegugGfuAfgCfaccussug	199	P-000067	gsgsagugCfuAftcCfagcguaugua	507	#N/A	#N/A	1165	18.72208	5.49196
SRS-000069	G-000015	usUfsguacAfuacCfugUfgGfuagcascu	201	P-000069	usgsuacCfaCfugfuaugggacaa	509	#N/A	#N/A	1169	19.26548	1.456436
SRS-000071	G-000016	usCfsuugUftcaUfcaCfugguagsgsc	203	P-000071	usasccacGfgUfaAfuaggacagaga	511	#N/A	#N/A	1172	13.3161	8.604597
SRS-000073	G-000064	usGfsauaaCfuugUfcCfaUfuaccgsug	205	P-000073	csgsguuaUfgCfaCfagaguuauca	513	35.23821	#N/A	1177	45.02429	4.735237
SRS-000074	G-000065	usCfsgauaAfcuUfcUfuUfuaccsgsu	206	P-000074	gsgsuauGfgAftcAfgaguuauca	514	9.343352	#N/A	1178	51.44863	1.590263
SRS-000075	G-000066	usAfscaaggAfuugGfuUfuCfucagsgsu	207	P-000075	usgsccagAfaUfcCfaggaucugua	515	4491.018	56880.83	2684	16.44153	9.013653
SRS-000078	G-000069	usGfsuuaAftcaUfaAfgGfugcgscsa	210	P-000078	gsccsagccCfcUfuAfuuguuuauca	518	#N/A	#N/A	2705	12.1747	1.347575
SRS-000079	G-000070	usCfsguuaAftcaUfaAfgGfugcgscsc	211	P-000079	csasggccCfuUfaUfuguuuauca	519	#N/A	#N/A	2706	41.82359	0.808165
SRS-000082	G-000017	usAfsuugUfuagGfuUfgCfaguuacusc	214	P-000082	gsusacugCfaAftcCfugacacaua	522	#N/A	#N/A	2749	23.07176	13.12197

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SRS-000086	G-000018	usUfsggucUfugagCfaUfuGfugucsgsg	218	P-000086	usgsacacAfaUfgCfucagacgcaa	526	#N/A	#N/A	2760	29.35791	15.60843
SRS-000087	G-000076	usUfscugcGfucugAfgCfaUfugugscsa	219	P-000087	ascascaaUfgCfuCfagacgcagaa	527	#N/A	#N/A	2762	10.5034	6.168005
SRS-000088	G-000077	usCfsuucUfegucUfgAfgCfaugugsgsu	220	P-000088	ascsaugCfuCfaCfagcagaga	528	#N/A	#N/A	2764	5.712127	7.947043
SRS-000093	G-000082	usGfsguccUfugauAfaCfuCfuguccsas	225	P-000093	gsgsacagAfgUfuAfucaaggcaca	533	163.9122	#N/A	2894	39.04343	3.861572
SRS-000106	G-000095	usUfscuauAfauggUfaGfuAfgcaguscsc	238	P-000106	ascsgucAfcUfaCfcauauuggaa	546	#N/A	#N/A	3219	13.31607	9.205419
SRS-000107	G-000096	usGfsuccaUfaugGfuAfgUfagcagusc	239	P-000107	csusgucAfcUfaCfcauauuggaca	547	#N/A	#N/A	3220	14.80472	4.612617
SRS-000108	G-000097	usUfscugucCfcauaAfuGfgUfagnagcsa	240	P-000108	csusacuaCfcAfuUfauaggacagaa	548	#N/A	#N/A	3223	16.80029	11.10403
SRS-000109	G-000098	usAfsaacUfuguccAfuAfaUfgguaggsa	241	P-000109	csusaccaUfuAfuGfagacagauua	549	#N/A	#N/A	3226	6.153194	7.498487
SRS-000110	G-000019	usUfsaacUfugucCfaUfaAfuagguagsgu	242	P-000110	usasceauUfaUfgCfagacagauua	550	#N/A	#N/A	3227	33.61694	3.644445
SRS-000111	G-000020	usCfscagCfugucCfaAfgUfucucscsu	243	P-000111	gsasagaaCfuUfgCfcaagcuugga	551	#N/A	#N/A	3276	17.35972	2.580181
SRS-000112	G-000021	usAfgaugAfcacCfcUfuGfgeaagsusu	244	P-000112	csusugccAfaCfcUfuggucaucua	552	8.297705	#N/A	3282	51.59325	4.521415
SRS-000113	G-000099	usAfsuagaUfgaccAfaGfcUfuggcasag	245	P-000113	usgsccaaCfcUfuGfgeaucuua	553	33.84077	659.9335	3284	45.41711	6.175907
SRS-000114	G-000100	usCfsauagAfuagCfaAfgCfugggcsasa	246	P-000114	gsccsaagCfuUfgGfucaucuanga	554	1.349305	11004.53	3285	58.87523	2.300955
SRS-000120	G-000022	usGfsguccGfacuaUfgCfuGfugugsgsu	252	P-000120	csasaccAfgCfaUfagucggacca	560	#N/A	#N/A	3309	10.24371	7.209576
SRS-000133	G-000118	usAfsuccaUfgguAfaAfcAfcacagsgsa	265	P-000133	csusugguGfuUfaUfaccuagguua	573	#N/A	#N/A	3738	17.57087	5.286225
SRS-000134	G-000119	usGfsggucCfcaugGfuAfaAfacaccsasa	266	P-000134	gsgsuguuAfuAfcCfauugauccca	574	#N/A	#N/A	3741	2.983854	2.420011
SRS-000135	G-000120	usGfsacauUfguguCfaGfgUfugcagsusa	267	P-000135	csusgcaaCfcUfgAfcacauugca	575	#N/A	#N/A	3778	9.608682	8.804995
SRS-000140	G-000125	usCfsaccaUfugggCfuAfgUfaucugsgsu	272	P-000140	asgsaauaCfuAfcCfcaauugguua	580	#N/A	#N/A	3991	19.11657	7.678151
SRS-000155	G-000140	usUfsaggaCfaccuGfuUfuCfuguuuscscu	287	P-000155	asasacagAfaUfaAfgugucuuua	595	#N/A	#N/A	4803	23.19757	11.52321
SRS-000168	G-000153	usUfsgagcAfuagCfuCfaGfugugcsasg	300	P-000168	gsccsaaccUfgAfcGfogaugcucua	608	#N/A	#N/A	5124	34.5264	2.589133
SRS-000175	G-000160	usUfsacaaUfgcuuCfcAfgGfacaunusc	307	P-000175	asasugucCfuGfgAfaageauugua	615	#N/A	#N/A	5505	15.05201	6.295908
SRS-000176	G-000161	usCfsagugAfuagAfaUfuUfagucscsu	308	P-000176	gsasucgaAfuGfuUfacaucacuga	616	#N/A	#N/A	5866	3.802795	3.789188

As used herein, "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "A" refers to 2'-fluoroadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "Cg" refers to guanosine-3'-phosphate; "G" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "s" refers to 3'-phosphorothioate. The "Transcript Start Site in NM_005577.4" is defined as the 5' position of a 21-mer target site in human transcript (NCBI Reference Sequence No: NM_005577.4). Note that the sense strand sequence is coupled to a targeting moiety (e.g., GalNAc or galactose) at the 3' end of the sense strand. MV: mean value. SD: standard deviation.

Table 6. % Change in Cynomolgus Monkey Circulating LP(a) Serum Concentration Following Single 3 mg/kg Dose

% Change in Cyno Serum Lipoprotein A concentration from Baseline (Day -1)																
SRS ID	SRS-000008	SRS-000009	SRS-000010	SRS-000011	SRS-000012	SRS-000013	SRS-000014	SRS-000015	SRS-000016	SRS-000017	SRS-000018	SRS-000019	SRS-000020	SRS-000021	SRS-000022	
	Position of 21mer Sense Strand															
Study Day	-1	Avg	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
		STDev	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
	3	Avg	-12.9	-8.9	-1.7	-4.5	-11.9	-5.3	8.8	0.2	-4.9	12.8	26.2	-0.1	7.3	22.3
		STDev	10.8	8.6	20.6	15.0	16.0	12.6	60.4	9.8	20.8	22.8	26.6	11.6	17.1	16.8
	7	Avg	-49.7	-15.7	-40.0	-19.2	-24.8	-15.2	-18.7	-26.6	-27.7	-35.1	-17.0	-3.1	-30.7	25.9
		STDev	5.3	7.9	10.3	18.0	10.7	14.7	46.4	12.5	16.3	15.5	20.3	22.1	15.2	13.6
	10	Avg	-67.5	-6.3	-63.9	-16.4	-31.6	-39.9	-22.5	-43.0	-45.9	-54.9	-4.1	-30.8	-63.6	16.1
		STDev	8.4	10.1	10.7	14.6	8.5	8.8	43.0	8.3	11.4	7.4	10.8	9.2	19.1	23.2
	14	Avg	-87.3	-31.8	-84.6	-35.8	-57.2	-63.2	-31.2	-68.1	-73.8	-74.6	-78.9	-22.7	-51.3	1.8
		STDev	4.4	5.3	4.5	4.4	6.1	7.1	48.1	4.8	3.1	7.6	15.0	19.5	13.7	18.2
	21	Avg	-98.9	-46.8	-98.7	-43.8	-71.0	-83.6	-47.5	-80.7	-87.6	-87.1	-90.1	-48.7	-65.7	-16.6
		STDev	2.2	9.9	2.7	10.3	7.3	3.1	37.1	5.1	1.2	3.8	7.2	10.8	12.8	14.2
	28	Avg	-100.0	-43.2	-100.0	-37.5	-77.4	-89.4	-47.0	-90.2	-92.6	-89.7	-94.9	-53.9	-80.3	-22.5
		STDev	0.0	14.8	0.0	16.5	5.2	3.5	44.4	7.0	2.4	3.9	4.3	17.0	13.3	15.4
	35	Avg	-100.0	-57.9	-100.0	-23.0	-76.5	-91.2	-55.0	-92.2	-95.2	-91.4	-96.5	-59.1	-83.4	-17.0
		STDev	0.0	17.9	0.0	11.8	6.4	3.1	35.3	5.6	1.3	3.1	3.1	11.1	11.2	20.9
42	Avg	-100.0	-58.4	-100.0	-31.6	-82.1	-97.5	-64.8	-94.1	-96.7	-93.0	-97.5	-71.8	-86.3	-23.4	
	STDev	0.0	14.9	0.0	7.6	7.2	3.0	16.2	4.2	2.2	3.9	3.1	20.0	9.7	11.2	
49	Avg	-100.0	-61.7	-100.0	-40.5	-83.9	-97.3	-65.5	-92.6	-98.5	-92.0	-97.4	-59.7	-81.8	-24.0	
	STDev	0.0	27.7	0.0	7.2	8.0	3.2	15.9	5.1	2.0	3.8	3.2	6.2	12.8	11.1	
56	Avg	-100.0	-51.1	-100.0	-40.4	-81.4	-95.7	-60.4	-91.9	-98.1	-91.3	-98.5	-46.6	-86.9	-26.7	
	STDev	0.0	13.9	0.0	5.5	9.7	3.2	16.3	5.8	2.3	3.7	1.9	16.7	9.9	11.1	
63	Avg	-100.0	-39.5	-100.0	-33.5	-81.4	-94.2	-57.0	-91.0	-98.3	-89.2	-96.5	-50.5	-85.7	-25.0	
	STDev	0.0	19.4	0.0	18.1	8.9	4.3	20.0	6.7	2.3	5.4	3.5	12.9	10.3	9.1	

	70	Avg	-100.0	-37.0	-100.0	-37.3	-81.3	-93.7	-58.4	-89.6	-97.6	-91.2	-95.3	-45.1	-82.3	-100.0	-9.9
		StdDev	0.0	21.8	0.0	8.1	11.6	5.9	18.9	7.8	1.7	4.0	4.2	14.4	14.8	0.0	17.8
	77	Avg	-100.0	-46.1	-100.0	-27.7	-78.0	-93.6	-55.6	-67.0	-96.5	-88.2	-94.2	-40.8	-81.9	-95.3	-6.8
		StdDev	0.0	38.8	0.0	6.2	14.3	4.5	13.0	42.5	2.6	5.0	5.3	12.1	13.9	9.4	31.3
	84	Avg	-100.0	-32.3	-100.0	-20.7	-77.6	-90.5	-52.0	-86.1	-96.0	-86.6	-93.8	-31.8	-78.0	-93.7	-13.9
		StdDev	0.0	24.0	0.0	14.5	13.4	7.6	14.4	10.8	1.2	5.0	4.6	13.1	17.6	12.5	24.9

Table 7. % Change in Cynomolgus Monkey Circulating LP(a) Serum Concentration Following Single 1 mg/kg Dose

% Change in Cyno Serum Lipoprotein A Concentration from Baseline (Day -1)													
SRS ID		SRS-000013		SRS-000016		SRS-000017		SRS-000018					
Position of 21mer Sense Strand		420		1172		2749		2760					
Study Day		Avg	StdDev	Avg	StdDev	Avg	StdDev	Avg	StdDev				
-1		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0				
3		8.5	2.7	0.5	13.0	7.6	6.7	-4.5	16.9				
7		-11.5	9.9	-13.2	25.0	-22.8	5.4	-26.1	12.2				
10		-28.2	8.3	-37.0	20.1	-41.0	6.4	-43.5	8.4				
14		-46.2	4.9	-59.4	16.4	-58.3	4.3	-63.4	5.2				
21		-65.3	26.5	-83.1	7.9	-85.6	3.2	-87.0	2.8				
28		-81.8	5.7	-88.9	3.4	-87.0	5.2	-91.6	1.6				
35		-79.9	2.6	-88.4	3.5	-83.5	7.3	-91.1	3.5				
42		-76.6	6.3	-89.3	3.6	-84.1	6.3	-91.1	4.1				
49		-75.8	10.0	-90.3	3.7	-84.3	5.5	-92.3	3.6				
56		-67.9	15.9	-90.6	3.9	-80.2	7.4	-91.0	4.4				
63		-70.9	13.6	-90.3	3.7	-78.0	6.8	-90.7	3.1				
70		-63.9	18.9	-90.2	3.7	-69.1	8.6	-86.6	4.5				

77	-62.6	18.8	-89.9	3.6	-71.1	6.2	-87.7	3.3
85	-62.2	12.7	-90.0	3.6	-67.1	8.2	-84.0	4.6
98	NA	NA	-88.0	3.9	NA	NA	-74.6	8.9
105	NA	NA	-88.5	4.4	NA	NA	-75.2	10.5
112	NA	NA	-86.6	4.7	NA	NA	-66.9	13.8
119	NA	NA	-84.1	6.1	NA	NA	-63.1	15.5
126	NA	NA	-80.3	9.2	NA	NA	-63.6	13.1
133	NA	NA	-79.8	10.2	NA	NA	-61.3	13.4
140	NA	NA	-79.9	10.7	NA	NA	-60.1	11.8

CLAIMS

WHAT IS CLAIMED IS:

1. A polynucleic acid molecule for modulating expression of lipoprotein(a) (Lp(a)) gene, comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 1-154.
2. The polynucleic acid of claim 1, wherein the sense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a nucleic acid sequence selected from SEQ ID NOs: 309-462.
3. The polynucleic acid molecule of any one of claims 1-2, wherein the antisense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, 20, 21, or 22 consecutive sequences of a nucleic acid sequence selected from SEQ ID NOs: 1-154, with no more than 1, 2, 3, or 4 mismatches.
4. The polynucleic acid molecule of any one of claims 1-3, wherein the sense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, or 20 consecutive sequences from a nucleic acid sequence selected from SEQ ID NOs: 309-462, with no more than 1, 2, 3, or 4 mismatches.
5. The polynucleic acid molecule of any one of claims 1-4, wherein the sense strand comprises one of SEQ ID NOs: 309-462 and the antisense strand comprises a nucleic acid sequence that is selected from SEQ ID NOs: 1-154.
6. The polynucleic acid molecule of any one of claims 1-5, wherein the sense strand comprises at least two consecutive modified internucleotide linkages at the 5' end.
7. The polynucleic acid molecule of any one of claims 1-6, wherein the antisense strand comprises at least two consecutive modified internucleotide linkages at the 5' end and/or 3' end.
8. The polynucleic acid molecule of any one of claims 6-7, wherein the modified internucleotide linkage is a phosphorothioate linkage.

9. The polynucleic acid molecule of claim 8, wherein the modified internucleotide linkage comprises a stereochemically enriched phosphorothioate internucleotide linkage.
10. The polynucleic acid molecule of any one of claims 8-9, wherein the modified internucleotide linkage is an S_P chiral internucleotide phosphorothioate linkage.
11. The polynucleic acid molecule of claim 10, wherein the polynucleic acid comprises a plurality of modified internucleotide linkages, and at least 1, 2, 3, or 4 of the plurality of modified internucleotide linkages are stereochemically enriched phosphorothioate internucleotide linkages.
12. The polynucleic acid molecule of any one of claims 9-11, wherein at least one stereochemically enriched phosphorothioate is disposed between two consecutive nucleosides that are two of six 5' or 3'-terminal nucleosides of the sense strand or the antisense strand.
13. The polynucleic acid molecule of any one of claims 1-12, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnnNfnnnnnNfnNfnNfnnnnnnn-3', wherein n stands for a 2'-O-methyl modified nucleotide, and wherein Nf stands for a 2'-fluoro modified nucleotide.
14. The polynucleic acid molecule of any one of claims 1-13, wherein the sense strand or antisense strand is about 19-25, or about 21-23 nucleotides in length.
15. The polynucleic acid molecule of any one of preceding claims, wherein the sense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 463-616.
16. The polynucleic acid molecule of any one of preceding claims, wherein the antisense strand comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 155-308.
17. The polynucleic acid molecule of any one of preceding claims, wherein the sense strand comprises a sequence selected from a nucleic acid sequence of SEQ ID NOs: 463-616, and the antisense strand comprises a sequence selected from a nucleic acid sequence of SEQ ID NOs: 155-308.
18. A polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises:

- (a) an antisense strand comprising the nucleotide sequence of UAGAUGACCAAGCUUGGCAGGUC (SEQ ID NO: 4) and a sense strand comprising the nucleotide sequence of CCUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 312);
- (b) an antisense strand comprising the nucleotide sequence of UAUAGAUGACCAAGCUUGGCAGG (SEQ ID NO: 5) and a sense strand comprising the nucleotide sequence of UGCCAAGCUUGGUCAUCUAUA (SEQ ID NO: 313);
- (c) an antisense strand comprising the nucleotide sequence of UCAUAGAUGACCAAGCUUGGCAG (SEQ ID NO: 6) and a sense strand comprising the nucleotide sequence of GCCAAGCUUGGUCAUCUAUGA (SEQ ID NO: 314);
- (d) an antisense strand comprising the nucleotide sequence of UCGACGGCAGUCCCUUCUGCGUC (SEQ ID NO: 11) and a sense strand comprising the nucleotide sequence of CGCAGAAGGGACUGCCGUCGA (SEQ ID NO: 319);
- (e) an antisense strand comprising the nucleotide sequence of UUCUAGGCUUGGAACCGGGGUA (SEQ ID NO: 18) and a sense strand comprising the nucleotide sequence of ACCCGGUUCCAAGCCUAGAA (SEQ ID NO: 326);
- (f) an antisense strand comprising the nucleotide sequence of UAGCCUCUAGGCUUGGAACCGGG (SEQ ID NO: 21) and a sense strand comprising the nucleotide sequence of CGGUUCCAAGCCUAGAGGCUA (SEQ ID NO: 329);
- (g) an antisense strand comprising the nucleotide sequence of UUUACCGUGGUAGCACUCCUGCA (SEQ ID NO: 44) and a sense strand comprising the nucleotide sequence of CAGGAGUGCUACCACGGUAAA (SEQ ID NO: 352);
- (h) an antisense strand comprising the nucleotide sequence of UUGUCCAUAACCGUGGUAGCACU (SEQ ID NO: 47) and a sense strand comprising the nucleotide sequence of UGCUACCACGGUAAUGGACAA (SEQ ID NO: 355);
- (i) an antisense strand comprising the nucleotide sequence of UCUCUGUCCAUAACCGUGGUAGC (SEQ ID NO: 49) and a sense strand comprising the nucleotide sequence of UACCACGGUAAUGGACAGAGA (SEQ ID NO: 357);

- (j) an antisense strand comprising the nucleotide sequence of UAUUGUGUCAGGUUGCAGUACUC (SEQ ID NO: 60) and a sense strand comprising the nucleotide sequence of GUACUGCAACCUGACACAAUA (SEQ ID NO: 368);
- (k) an antisense strand comprising the nucleotide sequence of UUGCGUCUGAGCAUUGUGUCAGG (SEQ ID NO: 64) and a sense strand comprising the nucleotide sequence of UGACACAAUGCUCAGACGCAA (SEQ ID NO: 372);
- (l) an antisense strand comprising the nucleotide sequence of UUAACUCUGUCCAUAUUGGUAGU (SEQ ID NO: 88) and a sense strand comprising the nucleotide sequence of UACCAUUAUGGACAGAGUUA (SEQ ID NO: 396);
- (m) an antisense strand comprising the nucleotide sequence of UCCAAGCUUGGCAAGUUCUCCU (SEQ ID NO: 89) and a sense strand comprising the nucleotide sequence of GAAGAACUUGCCAAGCUUGGA (SEQ ID NO: 397);
- (n) an antisense strand comprising the nucleotide sequence of UAGAUGACCAAGCUUGGCAAGUU (SEQ ID NO: 90) and a sense strand comprising the nucleotide sequence of CUUGCCAAGCUUGGUCAUCUA (SEQ ID NO: 398); or
- (o) an antisense strand comprising the nucleotide sequence of UGGUCCGACUAUGCUGGUGUGGU (SEQ ID NO: 98) and a sense strand comprising the nucleotide sequence of CACACCAGCAUAGUCGGACCA (SEQ ID NO: 406).
19. A polynucleic acid molecule for modulating expression of Lipoprotein(a) (Lp(a)) gene, wherein polynucleic acid molecule comprises:
- (a) an antisense strand comprising the nucleotide sequence of usAfsaugAfccaaGfcUfuGfgcaggsusc (SEQ ID NO: 158) and a sense strand comprising the nucleotide sequence of cscsugccAfaGfcUfuggucauca (SEQ ID NO: 466);
- (b) an antisense strand comprising the nucleotide sequence of usAfsuagaUfgaccAfaGfcUfuggcasgsg (SEQ ID NO: 159) and a sense strand comprising the nucleotide sequence of usgsccaaGfcUfuGfgucaucaua (SEQ ID NO: 467);
- (c) an antisense strand comprising the nucleotide sequence of usCfsauagAfugacCfaAfgCfuuggcsasg (SEQ ID NO: 160) and a sense strand comprising the nucleotide sequence of gscscaagCfuUfgGfucaucauga (SEQ ID NO: 468);

- (d) an antisense strand comprising the nucleotide sequence of usCfsgacgGfcaguCfcCfuUfcugcgsusc (SEQ ID NO: 165) and a sense strand comprising the nucleotide sequence of csgscagaAfgGfgAfcugccgucga (SEQ ID NO: 473);
- (e) an antisense strand comprising the nucleotide sequence of usUfscuagGfcuugGfaAfcCfggggusasa (SEQ ID NO: 172) and a sense strand comprising the nucleotide sequence of ascsccegGfuUfcCfaagccuagaa (SEQ ID NO: 480);
- (f) an antisense strand comprising the nucleotide sequence of usAfsgccuCfuaggCfuUfgGfaaccgsgsg (SEQ ID NO: 175) and a sense strand comprising the nucleotide sequence of csgsguucCfaAfgCfcuagaggcua (SEQ ID NO: 483);
- (g) an antisense strand comprising the nucleotide sequence of usUfsuaccGfugguAfgCfaCfuccugscsa (SEQ ID NO: 198) and a sense strand comprising the nucleotide sequence of csasggagUfgCfuAfccacgguaaa (SEQ ID NO: 506);
- (h) an antisense strand comprising the nucleotide sequence of usUfsguccAfuuacCfgUfgGfuagcascsu (SEQ ID NO: 201) and a sense strand comprising the nucleotide sequence of usgsuacCfaCfgGfuauggacaa (SEQ ID NO: 509);
- (i) an antisense strand comprising the nucleotide sequence of usCfsucugUfccauUfaCfcGfugguasgsc (SEQ ID NO: 203) and a sense strand comprising the nucleotide sequence of usascacGfgUfaAfggacagaga (SEQ ID NO: 511);
- (j) an antisense strand comprising the nucleotide sequence of usAfsuuguGfucagGfuUfgCfaguacsusc (SEQ ID NO: 214) and a sense strand comprising the nucleotide sequence of gsusacugCfaAfcCfugacacaaua (SEQ ID NO: 522);
- (k) an antisense strand comprising the nucleotide sequence of usUfsgcguCfugagCfaUfuGfugucasgsg (SEQ ID NO: 218) and a sense strand comprising the nucleotide sequence of usgsacacAfaUfgCfucagacgcaa (SEQ ID NO: 526);
- (l) an antisense strand comprising the nucleotide sequence of usUfsaacuCfugucCfaUfaAfgguasgsu (SEQ ID NO: 242) and a sense strand comprising the nucleotide sequence of usascgauUfaUfgGfacagaguuaa (SEQ ID NO: 550);

(m) an antisense strand comprising the nucleotide sequence of usCfscaggCfuuggCfaAfgUfucucscsu (SEQ ID NO: 243) and a sense strand comprising the nucleotide sequence of gsasagaaCfuUfgCfcaagcuugga (SEQ ID NO: 551);

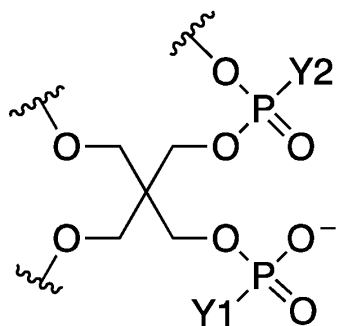
(n) an antisense strand comprising the nucleotide sequence of usAfsgaugAfccaaGfcUfuGfgcaagsusu (SEQ ID NO: 244) and a sense strand comprising the nucleotide sequence of csusugccAfaGfcUfuggucaucua (SEQ ID NO: 552); or

(o) an antisense strand comprising the nucleotide sequence of usGfsguccGfacuaUfgCfuGfgugugsgsu (SEQ ID NO: 252) and a sense strand comprising the nucleotide sequence of csascaccAfgCfaUfagucggacca (SEQ ID NO: 560),

wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “U” refers to uridine-3’-phosphate; “u” refers to 2’-O-methyluridine-3’-phosphate; “Uf” refers to 2’-fluorouridine-3’-phosphate; “T” refers to 5-methyluridine-3’-phosphate; “t” refers to 2’-O-methyl-5-methyluridine-3’-phosphate; “Tf” refers to 2’-fluoro-5-methyluridine-3’-phosphate; “s” refers to 3’-phosphorothioate.

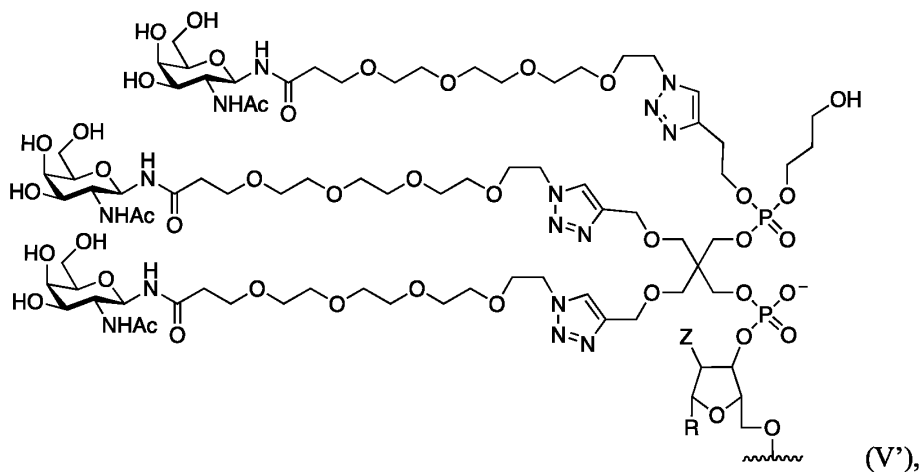
20. A polynucleic acid molecule conjugate for modulating expression of lipoprotein(a) gene (Lp(a)), wherein the polynucleic acid molecule conjugate comprises a polynucleic acid molecule of any one of claims [0220]-19 and an asialoglycoprotein receptor targeting moiety.
21. The polynucleic acid molecule conjugate of claim 20, wherein the asialoglycoprotein receptor targeting moiety comprises N-Acetylgalactosamine (GalNAc) or galactose.
22. The polynucleic acid molecule conjugate of one of claims 20-21, wherein the polynucleic acid molecule and the asialoglycoprotein receptor targeting moiety is coupled via a linker.
23. The polynucleic acid molecule conjugate of claim 22, wherein the linker is a cleavable linker.
24. The polynucleic acid molecule conjugate of any one of claims 21-23, wherein the GalNAc comprises an anomeric carbon bonded to trivalent, tetravalent linker, pentavalent, or hexavalent linker, wherein the anomeric carbon is part of a hemiaminal group.

25. The polynucleic acid molecule conjugate of any one of claims 22-24, wherein the linker comprises formula (IV) below,

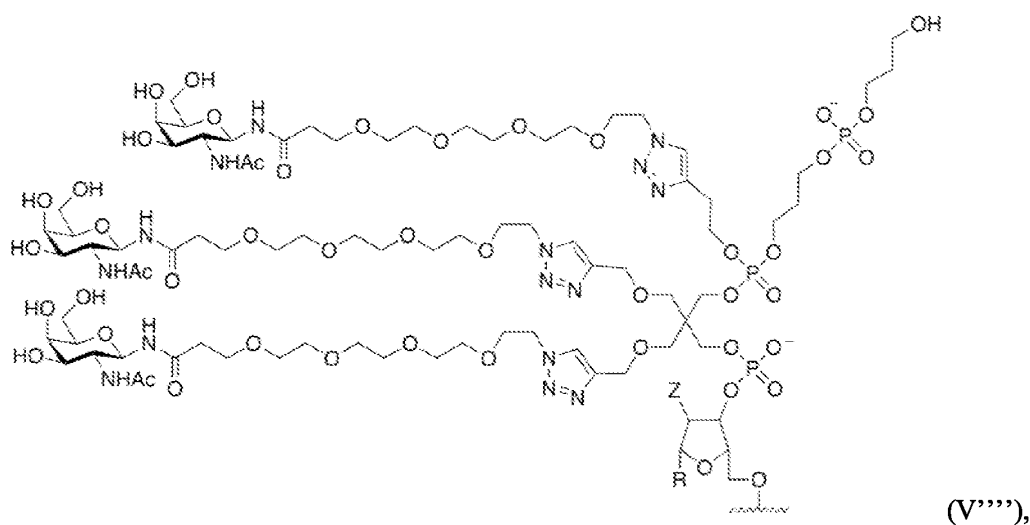


, wherein at least one of Y1 and Y2 is a nucleotide in the polynucleic acid molecule.

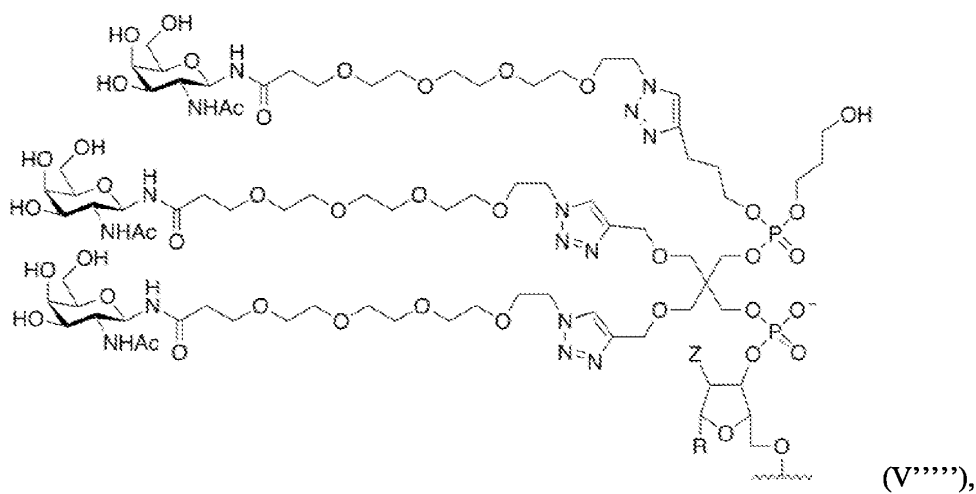
26. The polynucleic acid molecule conjugate of claim 25, wherein the Y1 is the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule.
27. The polynucleic acid molecule conjugate of any one of claims 22-26, wherein the linker and the asialoglycoprotein receptor targeting moiety with the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule are shown in Formula (V'), Formula (V'''), Formula (V'''''), or Formula (V'''''):



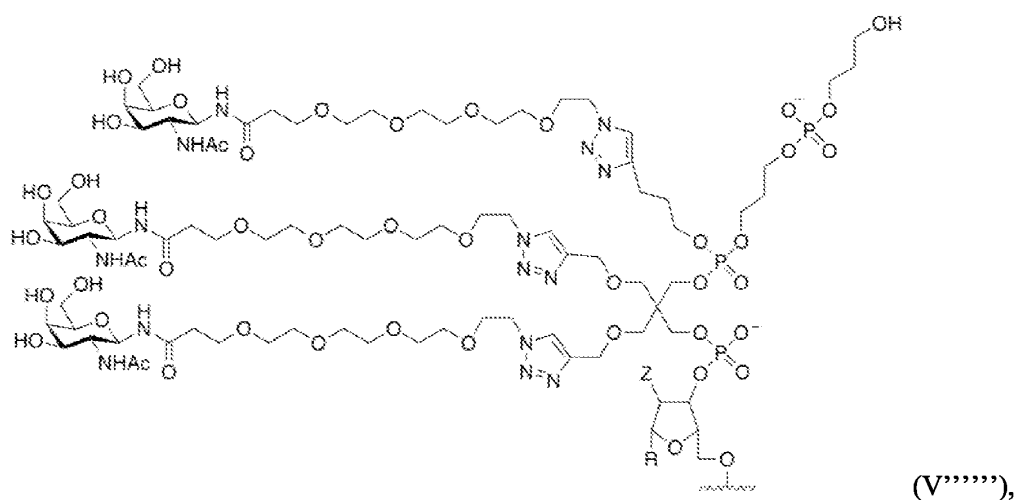
wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others;



wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

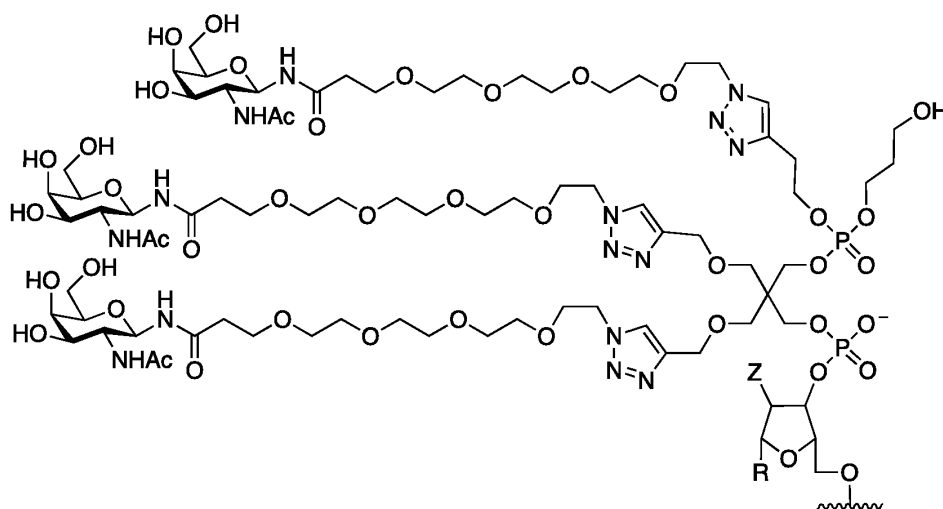


wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others; or



wherein Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

28. The polynucleic acid molecule conjugate of claim 27, wherein the linker and the asialoglycoprotein receptor targeting moiety with the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule are shown in Formula (V'):



(V'), wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

29. A pharmaceutical composition comprising a polynucleic acid molecule of any one of claims [0220]- 19 or a polynucleic acid molecule conjugate of any one of claims 20-28, and a pharmaceutically acceptable excipient.

30. The pharmaceutical composition of claim 29, wherein the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.
31. A method of modulating expression of lipoprotein(a) (Lp(a)) gene in a subject in need thereof, comprising:
- administering to the subject a polynucleic acid molecule of any one of claims 1-19, a polynucleic acid molecule conjugate of any one of claims 20-28, or a pharmaceutical composition of any one of claims 29-30, thereby modulating the expression of Lp(a) gene in the subject in need thereof.
32. A method for treating or preventing a cardiovascular disease or a lipid disorder, comprising
- administering to the subject a polynucleic acid molecule of any one of claims 1-19, a polynucleic acid molecule conjugate of any one of claims 20-28, or a pharmaceutical composition of any one of claims 29-30, thereby modulating the expression of Lp(a) gene in the subject in need thereof.
33. The method of any one of claims 31-32, wherein the polynucleic acid molecule is administered at a dose sufficient to decrease the expression of Lp(a) gene in a cell of said subject or to decrease plasma Lp(a) level of said subject by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% compared to a control.
34. The method of any one of claims 32-33, wherein the cardiovascular disease is coronary artery disease, acute myocardial infarction, asymptomatic carotid atherosclerosis, stroke, atrial fibrillation, hypercholesterolemia, or peripheral artery occlusive disease.
35. The method of any one of claims 32-33, wherein the lipid disorder is hyperlipidemia or hypercholesterolemia.