

POLYNUCLEIC ACID MOLECULES TARGETING *APOC3* AND USES THEREOF**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/371,326, filed on August 12, 2022, which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Apolipoprotein C3 (APOC3) is a protein encoded by the *APOC3* gene. APOC3 may be secreted by the liver as well as the small intestine, and may play an important role in inhibiting hepatic uptake of triglyceride-rich particles. Therefore, high plasma APOC3 correlates with high glyceride and an increased risk of developing cardiovascular diseases. Accordingly, there is a need for developing an effective APOC3 inhibitor without cytotoxicity. The polynucleic acid molecules, conjugates thereof, and methods described herein satisfy this need and provide related advantages.

INCORPORATION BY REFERENCE

[0003] 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

[0004] To meet the need for a more effective *APOC3* inhibitor, provided herein, in one aspect, is a polynucleic acid molecule for modulating expression of apolipoprotein C3 (*APOC3*) 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% identical to a nucleic acid sequence selected from SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563. 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: 1-108, 433-456, 529-534, and 553-563 with no more than 1, 2, 3, or 4 mismatches. 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: 217-324, 481-504, 541-546, and 575-585. In some cases, the sense strand comprises a nucleic acid sequence comprising at

least 14, 15, 16, 17, 18, 19, or 20 consecutive sequences of a nucleic acid sequence selected from SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches.

[0005] In some cases, the sense strand comprises a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563.

[0006] In some cases, the polynucleic acid molecule comprises (1) a 2'-fluoro modified nucleotides; (2) a 2'-O-methyl modified nucleotides; (3) 2'-deoxy modified nucleotides, or (4) a modified internucleotide linkage. In some cases, the polynucleic acid molecule comprise at least two consecutive modified internucleotide linkages at the 5' end or at the 3' end.

[0007] In some cases, the antisense strand comprises 5' - nNfnnnNfnNfNfnnnnNfnNfnnnnnn-3', 5' - nNfnnnNfnnnnnnNfnNfnnnnnn-3', 5' - nNfnnnnNfnnnnNfnNfnnnnnnnn-3', 5' - nNfnnnnNfnnnnNfnNfnNfnnnnnn-3', or 5' - nNfnnnnnnnnNfnNfnNfnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide. In some cases, the sense strand comprises 5'- nnnnnNfnNfnNfnnnnnnnn-3', 5'- nnnnnNfnNfNfNfnnnnnnnn-3', or 5'- nnnnnnnNfnNfNfnnnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide. In some cases, the sense strand of the polynucleic acid molecule comprises 5'- NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', the antisense strand of the polynucleic acid molecule comprises 5'- nNfnNfnNfnNfnNfnNfnNfnNfnNfn-3'; the sense strand of the polynucleic acid molecule comprises 5'- nnnnnNfnNfNfNfnnnnnnnn-3', the antisense strand of the polynucleic acid molecule comprises 5'- nNfnnnNfnNfNfnnnnNfnNfnnnnnn-3'; the sense strand of the polynucleic acid molecule comprises 5'- nnnnnnnNfnNfnnnnnnnn-3', wherein the antisense strand of the polynucleic acid molecule comprises 5'-nNfnnnnnnnnNfnNfnnnnnnnn-3'; the sense strand of the polynucleic acid molecule comprises 5'- nnnnnnnNfnNfnNfnnnnnnnn-3', the antisense strand of the polynucleic acid molecule comprises 5'-nNfnnnnnnnnNfnNfnNfnnnnnn-3'; or the sense strand of the polynucleic acid molecule comprises 5'- nnnnnNfnNfnNfnnnnnnnn-3', the antisense strand of the polynucleic acid molecule comprises 5'-nNfnnnnNfnnnnNfnNfnNfnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0008] In some cases, the modified internucleotide linkage is a phosphorothioate internucleotide linkage. In some cases, the modified internucleotide linkage comprises a stereochemically enriched phosphorothioate internucleotide linkage.

[0009] 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: 325-432, 505-528, 547-552, and 586-596. 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: 109-216, 457-480, 535-540, and 564-574. In some cases, the sense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596, and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574.

[0010] In another aspect, provided herein is polynucleic acid molecule for modulating expression of apolipoprotein C3 (*APOC3*) gene, wherein polynucleic acid molecule comprises: (a) an antisense strand comprising the nucleotide sequence of UUUCAGGGAACUGAAGCCAUCGG (SEQ ID NO:529) and a sense strand comprising the nucleotide sequence of GAUGGCUUCAGUCCCCUGAAA (SEQ ID NO:541); (b) an antisense strand comprising the nucleotide sequence of UGAAUACUGUCCCUUUUAAGCAA (SEQ ID NO:530) and a sense strand comprising the nucleotide sequence of GCUUAAAAGGGACAGUAUUCA (SEQ ID NO:542); (c) an antisense strand comprising the nucleotide sequence of UAGAAUACUGUCCCUUUUAAGCA (SEQ ID NO:531) and a sense strand comprising the nucleotide sequence of CUUAAAAGGGACAGUAUUCUA (SEQ ID NO:543); (d) an antisense strand comprising the nucleotide sequence of UUGAGAAUACUGUCCCUUUUAAG (SEQ ID NO:532) and a sense strand comprising the nucleotide sequence of UAAAAGGGACAGUAUUCUCAA (SEQ ID NO:544); (e) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO:533) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO:545); (f) an antisense strand comprising the nucleotide sequence of UCACUGAGAAUACUGUCCCUUUU (SEQ ID NO:534) and a sense strand comprising the nucleotide sequence of AAGGGACAGUAUUCUCAGUGA (SEQ ID NO:546); (g) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 554) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 576); (h) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUCAA (SEQ ID NO: 555) and a sense strand comprising the nucleotide sequence of GAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 577); (i) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUGAA (SEQ ID NO: 556) and a sense strand comprising the nucleotide sequence of CAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 578); (j) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUGCAA (SEQ ID NO: 557) and a sense strand comprising the nucleotide sequence of

GCAAGGGACAGUAUUCUCAGA (SEQ ID NO: 579); (k) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUCGAA (SEQ ID NO: 558) and a sense strand comprising the nucleotide sequence of CGAAGGGACAGUAUUCUCAGA (SEQ ID NO: 580); (l) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 559) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 581); (m) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUGAA (SEQ ID NO: 560) and a sense strand comprising the nucleotide sequence of CAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 582); (n) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 561) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 583); (o) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 562) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 584); or (p) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 563) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 585).

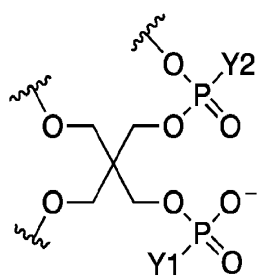
[0011] In another aspect, provided herein is polynucleic acid molecule for modulating expression of apolipoprotein C3 (APOC3) gene, wherein polynucleic acid molecule comprises: (a) an antisense strand comprising the nucleotide sequence of usUfsucagGfgaacUfgAfaGfccaucsgsg (SEQ ID NO:535) and a sense strand comprising the nucleotide sequence of gsauggcUfuCfaGfuuccugaaa (SEQ ID NO:547); (b) an antisense strand comprising the nucleotide sequence of usGfsaauaCfugucCfcUfuUfuaagsasa (SEQ ID NO:536) and a sense strand comprising the nucleotide sequence of gscsuuaaAfaGfgGfacaguuuca (SEQ ID NO:548); (c) an antisense strand comprising the nucleotide sequence of usAfsgaauAfcuguCfcCfuUfuuaagscsa (SEQ ID NO:537) and a sense strand comprising the nucleotide sequence of csusuaaaAfgGfgAfcaguuucua (SEQ ID NO:549); (d) an antisense strand comprising the nucleotide sequence of usUfsgagaAfuacuGfuCfcCfuuuuasasg (SEQ ID NO:538) and a sense strand comprising the nucleotide sequence of usasaaagGfgAfcAfguauucuaa (SEQ ID NO:550); (e) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO:539) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO:551); (f) an antisense strand comprising the nucleotide sequence of usCfsacugAfgaauAfcUfgUfccuususu (SEQ ID NO:540) and a sense strand comprising the nucleotide sequence of asasgggaCfaGfuAfuucucaguga (SEQ ID NO:552); (g) an

antisense strand comprising the nucleotide sequence of vpusCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO: 565) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 587); (h) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuucsasa (SEQ ID NO: 566) and a sense strand comprising the nucleotide sequence of gsasaaggGfaCfaGfuauucucaga (SEQ ID NO: 588); (i) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuugsasa (SEQ ID NO: 567) and a sense strand comprising the nucleotide sequence of csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 589); (j) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuugcsasa (SEQ ID NO: 568) and a sense strand comprising the nucleotide sequence of gscsaaggGfaCfaGfuauucucaga (SEQ ID NO: 590); (k) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuugcsasa (SEQ ID NO: 569) and a sense strand comprising the nucleotide sequence of csgsaaggGfaCfaGfuauucucaga (SEQ ID NO: 591); (l) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO: 570) and a sense strand comprising the nucleotide sequence of (invAb)asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 592); (m) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuugsasa (SEQ ID NO: 571) and a sense strand comprising the nucleotide sequence of (invAb)csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 593); (n) an antisense strand comprising the nucleotide sequence of usCfsugdAgdAauacUfgUfcCfcuuusasa (SEQ ID NO: 572) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 594); (o) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfscCfcuuusasa (SEQ ID NO: 573) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 595); or (p) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcsuuusasa (SEQ ID NO: 574) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 596), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "Tp" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers

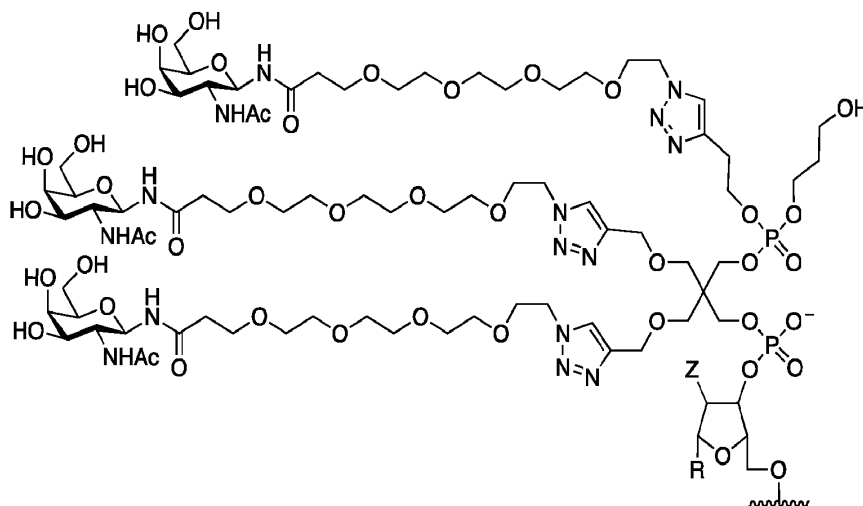
to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0012] In another aspect, provided herein is a polynucleic acid molecule conjugate for modulating expression of apolipoprotein C3 (*APOC3*) gene, 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.

[0013] In some cases, the polynucleic acid molecule and the asialoglycoprotein receptor targeting moiety is coupled via a linker. In some cases, the linker comprises formula (IV) below,

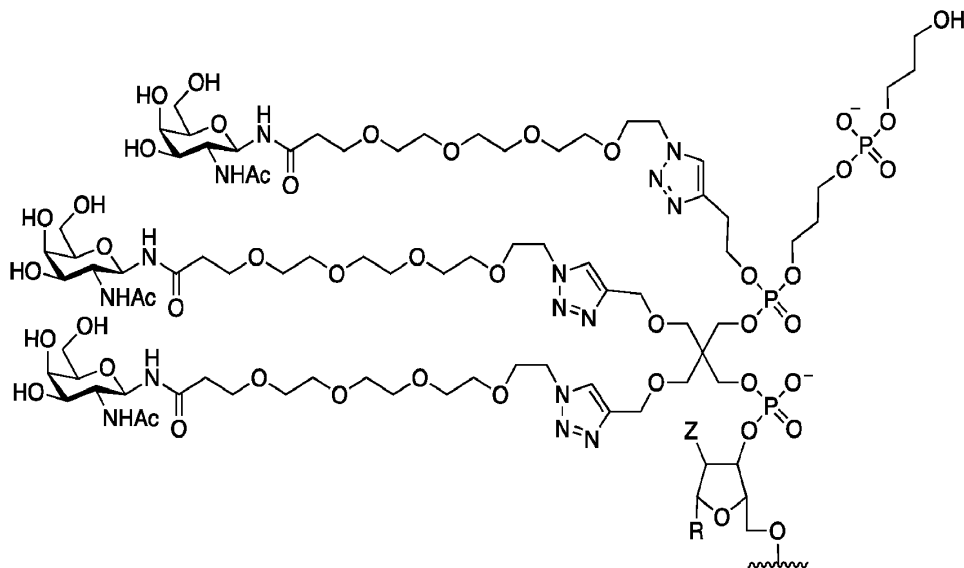


formula (IV), wherein at least one of Y1 and Y2 is a nucleotide in the polynucleic acid molecule. In some cases, the Y1 is the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule or the Y1 and Y2 are two consecutive nucleotides in the polynucleic acid molecule. In some instances, 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'):



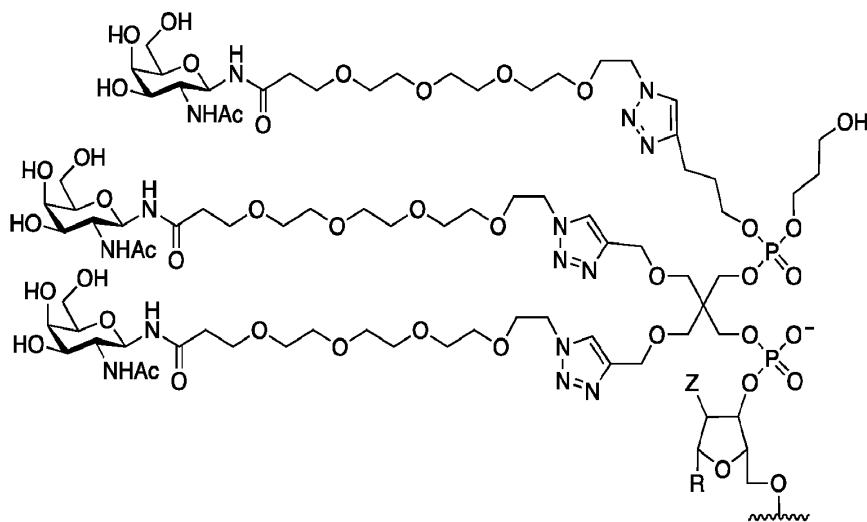
(V'), wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0014] In some instances, 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'''):



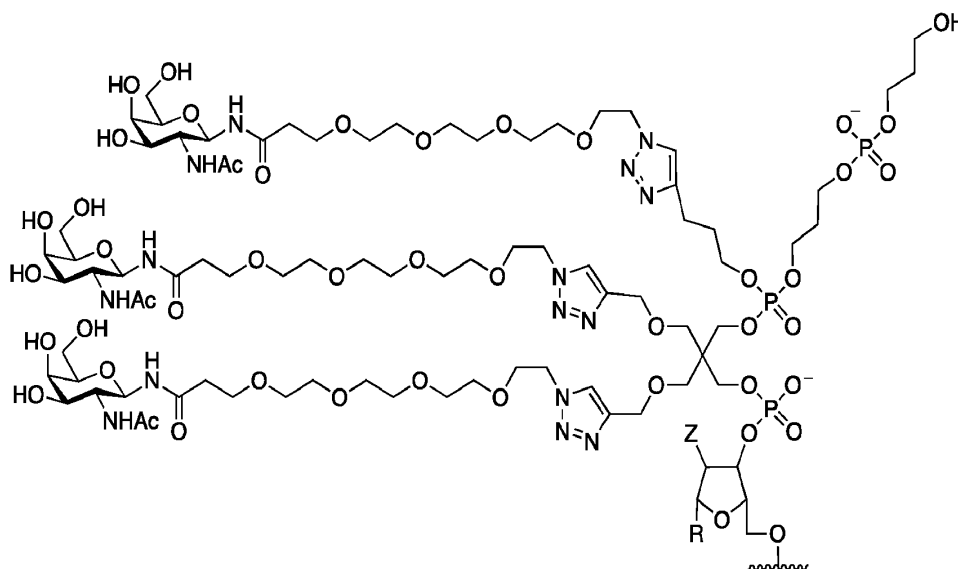
(V'''), wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0015] In some instances, 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 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.

[0016] In some instances, 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 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.

[0017] 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.

[0018] In some cases, the pharmaceutical composition is formulated as a nanoparticle formulation. In some cases, the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.

[0019] In another aspect, provided herein is a method of modulating expression of apolipoprotein C3 (*APOC3*) gene in a subject, comprising: administering to the subject a polynucleic acid molecule described herein or a polynucleic acid molecule conjugate described herein, or a pharmaceutical composition described herein, thereby modulating the expression of *APOC3* gene in the subject. In some cases, the subject in need thereof is diagnosed of, suffers from, or having a symptom of cardiovascular disease or hypertriglyceridemia.

[0020] In another aspect, provided herein is a method of modulating triglyceride level in a subject in need thereof, comprising: administering to the subject a polynucleic acid molecule described herein or a polynucleic acid molecule conjugate described herein, or a pharmaceutical composition described herein, thereby modulating triglyceride level in the subject. In some cases, the subject in need thereof is diagnosed of, suffers from, or having a symptom of cardiovascular disease or hypertriglyceridemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] 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.

[0022] FIGs. 1A-1X illustrate drug response curves for selected siRNAs for suppressing *APOC3* in primary hepatocytes. FIG.1A shows a drug response curve for SRS-000665. FIG.1B shows a drug response curve for SRS-000770. FIG.1C shows a drug response curve for SRS-000667. FIG.1D shows a drug response curve for SRS-000771. FIG.1E shows a drug response curve for SRS-000712. FIG.1F shows a drug response curve for SRS-000772. FIG.1G shows a drug response curve for SRS-000713. FIG.1H shows a drug response curve for SRS-000773. FIG.1I shows a drug response curve for SRS-000717. FIG.1J shows a drug response curve for SRS-000774. FIG.1K shows a drug response curve for SRS-000723. FIG.1L shows a drug response curve for SRS-000775. FIG.1M shows a drug response curve for SRS-000753. FIG.1N shows a drug response curve for SRS-000776. FIG.1O shows a drug response curve for SRS-000754. FIG.1P shows a drug response curve for SRS-000777. FIG.1Q shows a drug response curve for SRS-000755. FIG.1R shows a drug response curve for SRS-000778. FIG.1S shows a drug response curve for SRS-000756. FIG.1T shows a drug response curve for SRS-000779. FIG.1U shows a drug response curve for SRS-000757. FIG.1V shows a drug response curve for SRS-000780. FIG.1W shows a drug response curve for SRS-000758. FIG.1X shows a drug response curve for SRS-000781.

[0023] FIG. 2 shows plasma APOC3 protein expression relative to pre-dose levels following single dose administrations of siRNAs listed in Table 5 (SRS-000225 and SRS-000228 to SRS-000232) to cynomolgus monkeys.

[0024] FIGs. 3A-3C show liver APOC3 mRNA expression relative to pre-dose levels following single dose administrations of siRNAs listed in Table 5 (SRS-000225 and SRS-000228 to SRS-000232) to cynomolgus monkeys. FIG. 3A shows liver APOC3 mRNA expression relative to pre-

dose levels normalized to ACTB. FIG. 3B shows liver APOC3 mRNA expression relative to pre-dose levels normalized to ARL1. FIG. 3C shows liver APOC3 mRNA expression relative to pre-dose levels normalized to PPIA.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0025] APOC3 is a small protein with 79 amino acid residues that contains two amphipathic helices (*see e.g.*, Gangabadage et al., J Biol Chem. 2008;283(25):17416–17427). APOC3 is found to be on circulating lipoproteins including high-density lipoproteins (HDL), low-density lipoprotein (LDL), and triglyceride-rich lipoproteins (TRLs) such as chylomicrons (CM) and very low density lipoprotein (VLDL).

[0026] APOC3 is an important regulator in lipid (e.g., triglyceride) metabolism and cardiovascular diseases (pathological processes involved in atherosclerosis). Specifically, studies have shown that impaired catabolism of TRLs is linked to increased levels of plasma APOC3 (*see e.g.*, Boren et al., Arterioscler Thromb Vasc Biol. 2015;35(10):2218–2224). In addition to effects on lipid metabolism, APOC3 has been shown to directly influence development of atherosclerosis.

[0027] A lifelong deficiency of APOC3 may be cardioprotective. A reduction of plasma triglycerides by inhibition of APOC3 might be a promising strategy in management of severe hypertriglyceridemia or those with elevated plasma triglyceride.

[0028] Described herein is a polynucleic acid molecule for modulating expression of *APOC3* gene. In some aspects, the polynucleic acid molecule is a single-stranded nucleic acid molecule. In some aspects, the polynucleic acid molecule comprises a sense strand and an antisense strand, and wherein the polynucleic acid molecule comprises a nucleic acid sequence in Table 1, Table 3, Table 5, and Table 12. Accordingly, provided herein are various target regions of human *APOC3* mRNA the polynucleic acid molecule described herein hybridizes to. In some cases, provided herein is the sequences of the polynucleic acid molecule described herein. In some cases, provided herein is the possible modifications of the polynucleic acid molecule described herein. In some cases, provided herein is the possible conjugates of the polynucleic acid molecule described herein.

[0029] Also described herein is a method of modulating expression of *APOC3* gene in a subject. Described further herein is a method of modulating triglyceride in a subject in need thereof.

Definitions

[0030] 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.”

[0031] 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.

[0032] 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.

[0033] “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.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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).

[0038] As used herein, a “subject” can be any mammal, including a human and a non-human primate.

[0039] The term “condition,” as used herein, includes diseases, disorders, and susceptibilities. In some cases, the condition is an APOC3 related disorder or symptoms thereof.

[0040] 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.

[0041] 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.

[0042] “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.

[0043] 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.

[0044] 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 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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”.

[0049] 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 $N_1N_2N_3N_4N_5N_6N_7$, a consecutive sequence can be $N_1N_2N_3N_4$ or $N_3N_4N_5N_6$, but a sequence of $N_1N_3N_4N_5$ or $N_3N_4N_7$ cannot be a consecutive sequence.

[0050] As used herein, the term “negative control” refers to a subject or a cell receiving no treatment or placebo.

Polynucleic Acid Molecules

Target Regions of Polynucleic Acid Molecules

[0051] Described herein is a polynucleic acid molecule for modulating expression of *APOC3* gene. In some instances, the polynucleic acid molecule comprises a single-stranded nucleic acid molecule that hybridizes to certain regions of mRNA. In some instances, the polynucleic acid molecule is a double-stranded nucleic acid molecule. Also described herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein the polynucleic acid molecule is a double-stranded nucleic acid molecule, which comprises a sense strand and an antisense strand, and the antisense strand hybridizes to certain regions of *APOC3* mRNA.

[0052] In some aspects, the polynucleic acid molecule described herein hybridizes to certain regions of human *APOC3* mRNA. In some instances, the human *APOC3* mRNA is NM_000040.3. In some aspects, the polynucleic acid molecule described herein hybridizes to certain regions of non-human *APOC3* mRNA.

[0053] In some aspects, the polynucleic acid molecule described herein hybridizes to the 5' UTR region of human *APOC3* mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to the coding region of human *APOC3* mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to a portion of exon 1 of human *APOC3* mRNA. In some

aspects, the polynucleic acid molecule described herein hybridizes to a portion of exon 2 of human *APOC3* mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to a portion of exon 3 of human *APOC3* mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to a portion of exon 4 of human *APOC3* mRNA. In some aspects, the polynucleic acid molecule described herein hybridizes to the 3' UTR region of human *APOC3* mRNA.

[0054] In some aspects, the target region that the polynucleic acid molecule described herein hybridizes to is determined by *APOC3* silencing effectiveness and possible off-target effects. In some instances, the start of the target region fall between positions 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, or 91-100 of NM_000040.3. In some instances, the start of the target region fall between positions 101-110, 111-120, 121-130, 131-140, 141-150, 151-160, 161-170, 171-180, 181-190, or 191-200 of NM_000040.3. In some instances, the start of the target region fall between positions of 201-210, 211-220, 221-230, 231-240, 241-250, 251-260, 261-270, 271-280, 281-290, or 291-300 of NM_000040.3. In some instances, the start of the target region fall between positions 301-310, 311-320, 321-330, 331-340, 341-350, 351-360, 361-370, 371-380, 381-390, or 391-400 of NM_000040.3. In some instances, the start of the target region fall between positions 401-410, 411-420, 421-430, 431-440, 441-450, 451-460, 461-470, 471-480, 481-490, or 491-500 of NM_000040.3. In some instances, the start of the target region fall between positions 501-510, 511-520, 521-530, or 531-535 of NM_000040.3.

Structure of Polynucleic Acid Molecules

[0055] Single-stranded nucleic acid molecule

[0056] Described herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein the polynucleic acid molecule comprises a single-stranded nucleic acid molecule that is reverse complementary to the target region of *APOC3* mRNA as described above.

[0057] In some aspects, the polynucleic acid molecule described herein is not 100% complementary to the target region of *APOC3* mRNA. Accordingly, in some instances, the polynucleic acid molecule described herein is about 95% complementary to the target region of *APOC3* mRNA. In some instances, the polynucleic acid molecule described herein is about 90% complementary to the target region of *APOC3* mRNA. In some instances, the polynucleic acid molecule described herein is about 85% complementary to the target region of *APOC3* mRNA. In some instances, the polynucleic acid molecule described herein is about 80% complementary to the target region of *APOC3* mRNA. In some instances, the polynucleic acid molecule described herein is about 75% complementary to the target region of *APOC3* mRNA. In some instances, the

polynucleic acid molecule described herein is about 70% complementary to the target region of *APOC3* mRNA.

[0058] In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence in Table 1, Table 3, Table 5, and Table 12. 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 3, Table 5, and Table 12. 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: 217-324, 481-504, 541-546, and 575-585. 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: 541-546.

[0059] 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 3, Table 5, and Table 12, 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: 217-324, 481-504, 541-546, and 575-585, 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: 541-546, excluding overhangs.

[0060] 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504,

541-546, and 575-585 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches.

[0061] 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 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 NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches.

[0062] 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 3, Table 5, and Table 12 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 NOs: 217-324, 481-504, 541-546, and 575-585 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 NOs: 541-546 without overhangs with no more than 1, 2, 3, or 4 mismatches.

[0063] 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.

[0064] 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.

[0065] Double-stranded nucleic acid molecule

[0066] Further described herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein the polynucleic acid molecule is a double-stranded molecule that comprises a sense strand and an antisense strand, and the antisense strand is reverse complementary to the target region of *APOC3* mRNA as described above.

[0067] In some aspects, the antisense strand described herein is 100% complementary to the target region of *APOC3* mRNA. In other aspects, the antisense strand described herein is not 100% complementary to the target region of *APOC3* mRNA. Accordingly, in some instances, the antisense strand described herein is about 95% complementary to the target region of *APOC3* mRNA. In some aspects, the antisense strand described herein is about 90% complementary to the target region of *APOC3* mRNA. In some aspects, the antisense strand described herein is about 85% complementary to the target region of *APOC3* mRNA. In some aspects, the antisense strand described herein is about 80% complementary to the target region of *APOC3* mRNA. In some aspects, the antisense strand described herein is about 75% complementary to the target region of *APOC3* mRNA. In some aspects, the antisense strand described herein is about 70% complementary to the target region of *APOC3* mRNA.

[0068] In some aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence in Table 1, Table 3, Table 5, and Table 12. 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, Table 3, Table 5, and Table 12. 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: 217-324, 481-504, 541-546, and 575-585. In some instances, the antisense 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: 1-108, 433-456, 529-534, and 553-563. 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: 541-546. In some instances, the antisense 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: 529-534.

[0069] In yet other aspects, the polynucleic acid molecule described herein comprises a nucleic acid sequence comprising 14 consecutive sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 14 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 14 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 sequences out of the sequences in

Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 15 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 15 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 16 consecutive sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 16 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 16 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 17 consecutive sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 17 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 17 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 18 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 18 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 19 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 19 consecutive sequences of SEQ

ID NOs: 1-108, 433-456, 529-534, and 553-563 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 sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 20 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 20 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 21 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 21 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 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 sequences out of the sequences in Table 1, Table 3, Table 5, and Table 12 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 22 consecutive sequences of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 22 consecutive sequences of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563 with no more than 1, 2, 3, or 4 mismatches.

[0070] In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 15 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 15 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 16 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 16 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 17 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid

sequence comprising 17 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 18 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 18 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 19 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 19 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 20 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 20 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 21 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 21 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the sense strand described herein comprises a nucleic acid sequence comprising 22 consecutive sequences of SEQ ID NOs: 541-546 with no more than 1, 2, 3, or 4 mismatches. In some aspects, the antisense strand described herein comprises a nucleic acid sequence comprising 22 consecutive sequences of SEQ ID NOs: 529-534 with no more than 1, 2, 3, or 4 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 polynucleotide 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 polynucleotide molecule described herein comprises one or more sugar-modified nucleotide. In some aspects, the sugar-modified nucleotide is a 2'-fluoro 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'-O-methyl modified nucleotide or 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, 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). 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 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.

[0075] In some aspects, the polynucleotide 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 instances, the heterocyclic substitution includes imidazole, and pyrrolidino. In some aspects, the modified sugarphosphate is thiophosphoramidate. In some aspects, the modified sugarphosphate is peptide nucleic acid (PNA).

[0076] In some aspects, the polynucleotide molecule described herein comprises one or more backbone-modified nucleotide. In some aspects, the modified backbone is a methylphosphonate. In some aspects, the modified backbone is phosphorothioate. In some aspects, the modified backbone is a 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, phosphoramidates.

[0077] In some aspects, the modified nucleotide comprises a modified guanine (e.g., inosine) or one or more of any types of unnatural nucleic acids.

[0078] 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.

[0079] 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.

[0080] 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 *S_p*-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 *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 *R_p*-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.

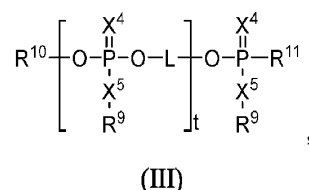
[0081] In some aspects, the polynucleotide molecule described herein comprises one or more purine modification. In some aspects, the purine modification described herein is 2,6-diaminopurine. In some aspects, the purine modification described herein is 3-deaza-adenine. In some aspects, the purine modification described herein is 7-deaza-guanine. In some aspects, the purine modification described herein is 8-azido-adenine.

[0082] 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.

[0083] In some case, 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] The polynucleotide molecule described herein may contain a strand including a seed region including a hypoxanthine nucleobase-containing nucleoside (e.g., inosine).

[0088] 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.

The Amount and Location of Modifications

[0089] 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.

[0090] In some aspects, the one or more types of modifications described herein occurs at different positions within the polynucleotide molecule described herein. In some aspects, the one or more types of modifications described herein occurs in the seed region within the polynucleotide molecule described herein. In some aspects, the one or more types of modifications described herein occurs at 3' terminal of the polynucleotide molecule described herein. In some aspects, the one or more types of modifications described herein occurs at 5' terminal of the polynucleotide molecule described herein. In some aspects, the one or more types of modifications described

herein occurs dispersedly within the polynucleotide molecule described herein. In some aspects, the one or more types of modifications described herein occurs in clusters within the polynucleotide molecule described herein.

Specific Modification Patterns

[0091] 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.

[0092] 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.

[0093] 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.

[0094] In some aspects, the antisense strand comprises 5' - nNfnnnNfnNfNfnnnnNfnNfnnnnnnn-3'. In some aspects, the antisense strand comprises 5' - nNfnnnNfnnnnnnnNfnNfnnnnnnn-3'. In some aspects, the antisense strand comprises 5' - nNfnnnnNfnnnnNfnNfnnnnnnnnn-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.

[0095] In some aspects, the sense strand comprises 5' - nnnnnnNfnNfnNfnnnnnnnnn-3'. In some aspects, the sense strand comprises 5' - nnnnnnNfnNfNfNfnnnnnnnnn-3'. In some aspects, the sense strand comprises 5' - nnnnnnnNfNfNfnnnnnnnnn-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.

[0096] 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.

[0097] 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.

[0098] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5' - NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises 5' - nNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0099] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5' - NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises 5' - nNfnNfnNfnNfnNfnNfnNfnNfnNf-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'-nNfnNfnNfnNfnNfnNfnNfnNfnNfn -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.

[0100] 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 19**.

Table 19. Nucleotide Modification Patterns

Pattern Name	Pattern
Type I for sense strand	5'- NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNf-3'
Type I for antisense strand	5'-nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3'
Type II for sense strand	5'- nsnsnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfn -3'
Type II for antisense strand	5'- nsNfsnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn - 3'
Type III for sense strand	5'- nsnsnnnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfn -3'
Type III for antisense strand	5'- nsNfsnnnnnnnnNfnNfnNfnNfnNfnNfnNfsnsn -3'
Type IV for sense strand	5'- nsnsnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfn -3'
Type IV for antisense strand	5'- nsNfsnnnnnnnnNfnNfnNfnNfnNfnNfnNfsnsn -3'
Type V for sense strand	5'- nsnsnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfn -3'
Type V for antisense strand	5'-_nsNfsnnnnNfnNfnNfnNfnNfnNfnNfsnsn -3'
Type VI for sense strand	5'- nnnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfn-invdN-invdN -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, "invdN" stands for an inverted deoxy-nucleotide.

[0101] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 and an antisense strand comprises a nucleic acid sequence of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585, an antisense strand comprises a nucleic acid sequence of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563, and wherein the sense and/or antisense strand is modified in Type I modification pattern specified in **Table 19**. In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 541-546 and an antisense strand comprises a nucleic acid sequence of SEQ ID NOs: 529-534. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 541-546, an antisense strand comprises a nucleic acid sequence of SEQ

wherein the sense and/or antisense strand is modified in Type II modification pattern specified in **Table 19**.

[0108] 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.

[0109] 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.

[0110] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnnnNfnNfnnnnnnnnn -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.

[0111] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'- nnnnnnnnNfnNfnnnnnnnnn -3', wherein the antisense strand comprises 5'- nNfnnnnnnnnnNfnNfnnnnnnnnn -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'- nnnnnnnnNfnNfnnnnnnnnn -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.

[0112] 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 19**.

[0113] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563, and wherein the sense and/or antisense strand is modified in Type III modification pattern specified in **Table 19**. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 541-546, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 529-534, and

wherein the sense and/or antisense strand is modified in Type III modification pattern specified in **Table 19**.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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 19**.

[0119] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563, and wherein the sense and/or antisense strand is modified in Type IV modification pattern specified in **Table 19**. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 541-546, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 529-534, and

wherein the sense and/or antisense strand is modified in Type IV modification pattern specified in **Table 19**.

[0120] 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.

[0121] 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.

[0122] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnnNfnnnnnNfnNfnNfnnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[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'-nNfnnnnnNfnnnnnNfnNfnNfnnnnnnn-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'-nNfnnnnnNfnnnnnNfnNfnNfnnnnnnn-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.

[0124] 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 19**.

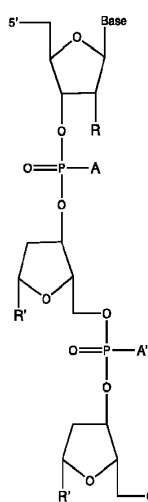
[0125] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563, and wherein the sense and/or antisense strand is modified in Type V modification pattern specified in **Table 19**. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 541-546, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 529-534, and

wherein the sense and/or antisense strand is modified in Type V modification pattern specified in Table 19.

[0126] 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.

[0127] 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.

[0128] In some aspects, described herein is a specific modification pattern, wherein the sense strand comprises 5' - nnnnnnNfNfNfnnnnnnnnnn-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.



wherein R is a moiety that corresponds to the sugar modification described 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.

[0129] In some aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 1-108, 433-456,

529-534, and 553-563, and wherein the sense strand is modified in Type VI modification pattern specified in **Table 19** or as described in the preceding paragraph. In other aspects, the polynucleotide molecule provided herein comprises a sense strand comprising a nucleic acid sequence of SEQ ID NOs: 541-546, and/or an antisense strand comprising a nucleic acid sequence of SEQ ID NOs: 529-534, and wherein the sense strand is modified in Type VI modification pattern specified in **Table 19** or as described in the preceding paragraph.

[0130] Described herein is a polynucleic acid molecule, whose sense strand comprises a nucleic acid sequence that is at least 80% identical to a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596. Described herein is a polynucleic acid molecule, whose sense strand comprises a nucleic acid sequence that is at least 85% identical to a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596. Described herein is a polynucleic acid molecule, whose sense strand comprises a nucleic acid sequence that is at least 90% identical to a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596. Described herein is a polynucleic acid molecule, whose sense strand comprises a nucleic acid sequence that is at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596.

[0131] Described herein is a polynucleic acid molecule, which antisense strand comprises a nucleic acid sequence that is at least 80% identical to a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574. Described herein is a polynucleic acid molecule, which antisense strand comprises a nucleic acid sequence that is at least 85% identical to a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574. Described herein is a polynucleic acid molecule, which antisense strand comprises a nucleic acid sequence that is at least 90% identical to a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574. Described herein is a polynucleic acid molecule, which antisense strand comprises a nucleic acid sequence that is at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574.

[0132] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usUfsucagGfgaacUfgAfaGfccaucsgsg (SEQ ID NO:535) and a sense strand comprising the nucleotide sequence of gsauggcUfuCfaGfuuccugaaa (SEQ ID NO:547), wherein "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to

guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0133] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usGfsaaauCfugucCfcUfuUfuaagcsasa (SEQ ID NO:536) and a sense strand comprising the nucleotide sequence of gscsuuaaAfaGfgGfacagauuca (SEQ ID NO:548), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0134] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usAfsaaauAfcuguCfcCfuUfuaagcsa (SEQ ID NO:537) and a sense strand comprising the nucleotide sequence of csusuaaaAfgGfgAfcagauuca (SEQ ID NO:549), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "TP" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0135] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usUfsgagaAfuacuGfuCfcCfuuuuasag (SEQ ID NO:538) and a sense strand comprising the nucleotide sequence of usasaagGfgAfcAfguauucuaa (SEQ ID NO:550), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0136] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfuuuusasa (SEQ ID NO:539) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO:551), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0137] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsacugAfgaauAfcUfgUfccccusus (SEQ ID NO:540) and a sense strand comprising the nucleotide sequence of asasgggaCfaGfuAfuucucaguga (SEQ ID NO:552), where “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “dA” refers to 2’-deoxyadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “dC” refers to 2’-deoxycytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “dG” refers to 2’-deoxyguanosine-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; “dT” refers to 2’-deoxythymidine-3’-phosphate; “s” refers to 3’-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5’-vinylphosphonate modified nucleotide.

[0138] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of vpusCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO: 565) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 587), where “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “dA” refers to 2’-deoxyadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “dC” refers to 2’-deoxycytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “dG” refers to 2’-deoxyguanosine-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; “dT” refers to 2’-deoxythymidine-3’-phosphate; “s” refers to 3’-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5’-vinylphosphonate modified nucleotide.

[0139] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuucsasa (SEQ ID NO: 566) and a sense strand comprising the nucleotide sequence of gsasaaggGfaCfaGfuauucucaga (SEQ ID NO: 588), where

“A” refers to adenosine-3'-phosphate; “a” refers to 2'-O-methyladenosine-3'-phosphate; “Af” refers to 2'-fluoroadenosine-3'-phosphate; “dA” refers to 2'-deoxyadenosine-3'-phosphate; “C” refers to cytidine-3'-phosphate; “c” refers to 2'-O-methylcytidine-3'-phosphate; “Cf” refers to 2'-fluorocytidine-3'-phosphate; “dC” refers to 2'-deoxycytidine-3'-phosphate; “G” refers to guanosine-3'-phosphate; “g” refers to 2'-O-methylguanosine-3'-phosphate; “Gf” refers to 2'-fluoroguanosine-3'-phosphate; “dG” refers to 2'-deoxyguanosine-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; “dT” refers to 2'-deoxythymidine-3'-phosphate; “s” refers to 3'-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5'-vinylphosphonate modified nucleotide.

[0140] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuugsasa (SEQ ID NO: 567) and a sense strand comprising the nucleotide sequence of csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 589), where “A” refers to adenosine-3'-phosphate; “a” refers to 2'-O-methyladenosine-3'-phosphate; “Af” refers to 2'-fluoroadenosine-3'-phosphate; “dA” refers to 2'-deoxyadenosine-3'-phosphate; “C” refers to cytidine-3'-phosphate; “c” refers to 2'-O-methylcytidine-3'-phosphate; “Cf” refers to 2'-fluorocytidine-3'-phosphate; “dC” refers to 2'-deoxycytidine-3'-phosphate; “G” refers to guanosine-3'-phosphate; “g” refers to 2'-O-methylguanosine-3'-phosphate; “Gf” refers to 2'-fluoroguanosine-3'-phosphate; “dG” refers to 2'-deoxyguanosine-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; “dT” refers to 2'-deoxythymidine-3'-phosphate; “s” refers to 3'-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5'-vinylphosphonate modified nucleotide.

[0141] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuugcsasa (SEQ ID NO: 568) and a sense strand comprising the nucleotide sequence of gscsaaggGfaCfaGfuauucucaga (SEQ ID NO: 590), where “A” refers to adenosine-3'-phosphate; “a” refers to 2'-O-methyladenosine-3'-phosphate; “Af” refers to 2'-fluoroadenosine-3'-phosphate; “dA” refers to 2'-deoxyadenosine-3'-phosphate; “C” refers to cytidine-3'-phosphate; “c” refers to 2'-O-methylcytidine-3'-phosphate; “Cf” refers to 2'-fluorocytidine-3'-phosphate; “dC” refers to 2'-deoxycytidine-3'-phosphate; “G” refers to

guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0142] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuucgsasa (SEQ ID NO: 569) and a sense strand comprising the nucleotide sequence of csgsaaggGfaCfaGfuauucucaga (SEQ ID NO: 591), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0143] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO: 570) and a sense strand comprising the nucleotide sequence of (invAb)asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 592), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "Tp" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0144] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuugsasa (SEQ ID NO: 571) and a sense strand comprising the nucleotide sequence of (invAb)csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 593), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "Tp" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0145] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugdAgdAauacUfgUfcCfcuuuusasa (SEQ ID NO: 572) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 594), where "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Af" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "Tp" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

[0146] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfscCfcuuuusasa (SEQ ID NO: 573) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 595), where “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “dA” refers to 2’-deoxyadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “dC” refers to 2’-deoxycytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “dG” refers to 2’-deoxyguanosine-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; “dT” refers to 2’-deoxythymidine-3’-phosphate; “s” refers to 3’-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5’-vinylphosphonate modified nucleotide.

[0147] Further provided herein is a polynucleic acid molecule for modulating expression of *APOC3* gene, wherein polynucleic acid molecule comprises an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcsuuuusasa (SEQ ID NO: 574) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 596), where “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “dA” refers to 2’-deoxyadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “dC” refers to 2’-deoxycytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “dG” refers to 2’-deoxyguanosine-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; “dT” refers to 2’-deoxythymidine-3’-phosphate; “s” refers to 3’-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5’-vinylphosphonate modified nucleotide.

Conjugation

Targeting moiety

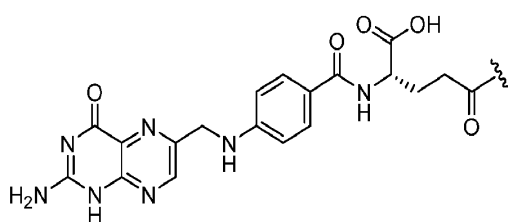
[0148] In certain aspects, the polynucleotide molecule described herein is coupled or conjugated with one or more targeting moieties to form a polynucleotide-targeting moiety conjugate molecule. In some instances, a targeting moiety is selected based on its ability to target the conjugate molecule described 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 conjugated with N-acetyl galactosamine (GalNAc) can target hepatocytes expressing asialoglycoprotein (ASGP-R). 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.

[0149] 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.

[0150] 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).

[0151] 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.

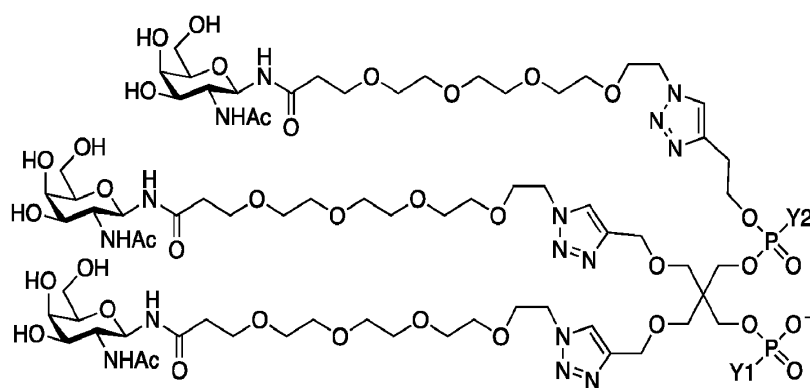
[0152] Other peptides for use as a targeting auxiliary moiety in polynucleotide molecule described herein can be selected from KiSS peptides and analogs, urotensin II peptides and analogs, GnRH I and II peptides and analogs, depreotide, vapreotide, vasoactive intestinal peptide (VIP), cholecystokinin (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(psi)), 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 adenylyl cyclase type I receptor (PAC1), fibrin α -chain, peptides derived from phage display libraries, and conservative substitutions thereof.

[0153] 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''', V''') through -LinkA-.

[0154] 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). In some aspects, an asialoglycoprotein receptor ligand (e.g., GalNAc) comprises an anomeric carbon bonded to trivalent, tetravalent linker, pentavalent, or hexavalent linker, wherein the anomeric carbon is part of a hemiaminal group. 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.

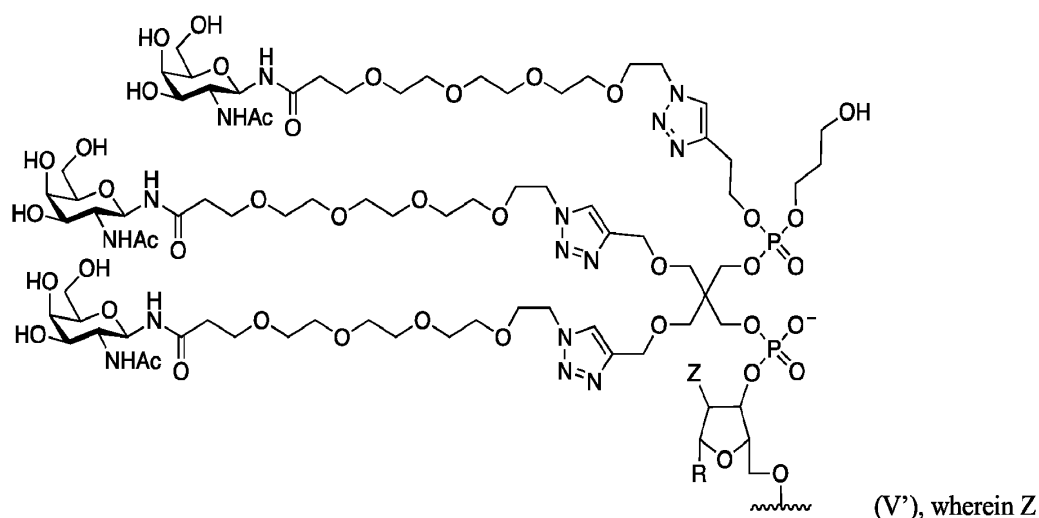
[0155] In some aspects, the linker and three asialoglycoprotein receptor targeting moieties, each of which comprises GalNAc, are as shown in Formula (V). In some instances, the conjugate described herein only comprises one asialoglycoprotein receptor targeting moiety, so the conjugate comprises a structure 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.



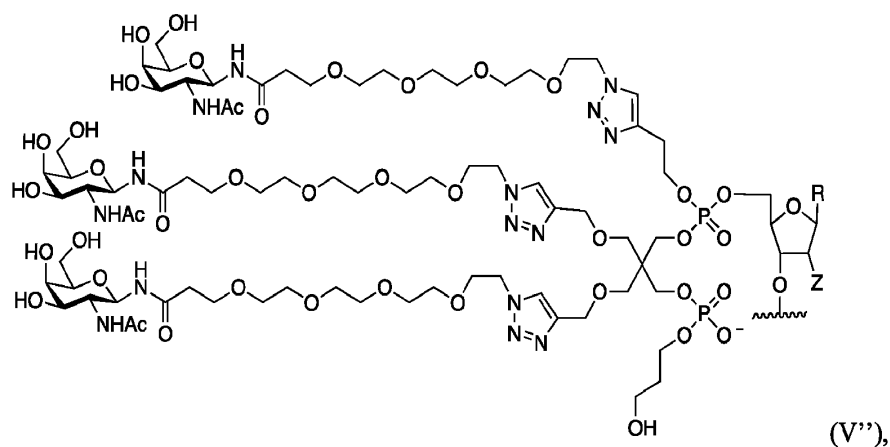
(V),

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.

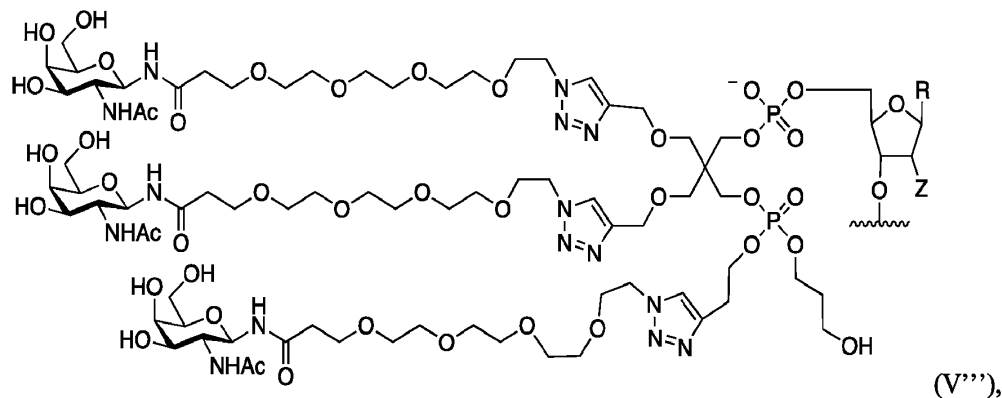
[0156] In some aspects, the linker and the targeting moieties described herein are conjugated to 3' end of the sense strand (e.g., as shown in Formula (V', V''', V''', V''''')). In some aspects, the linker and the targeting moieties described herein are conjugated to 5' end of the sense strand (e.g., 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''')).



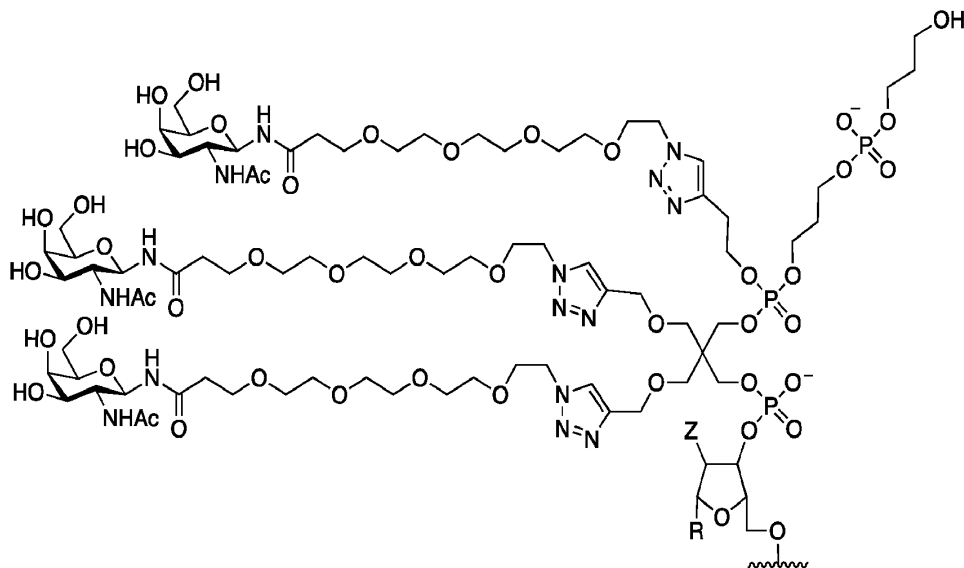
in formula (V') corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl), and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



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.

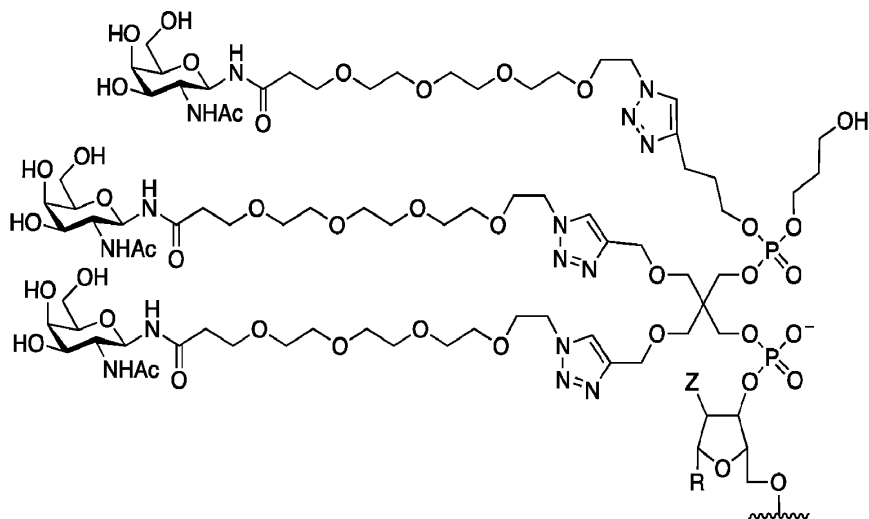


wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



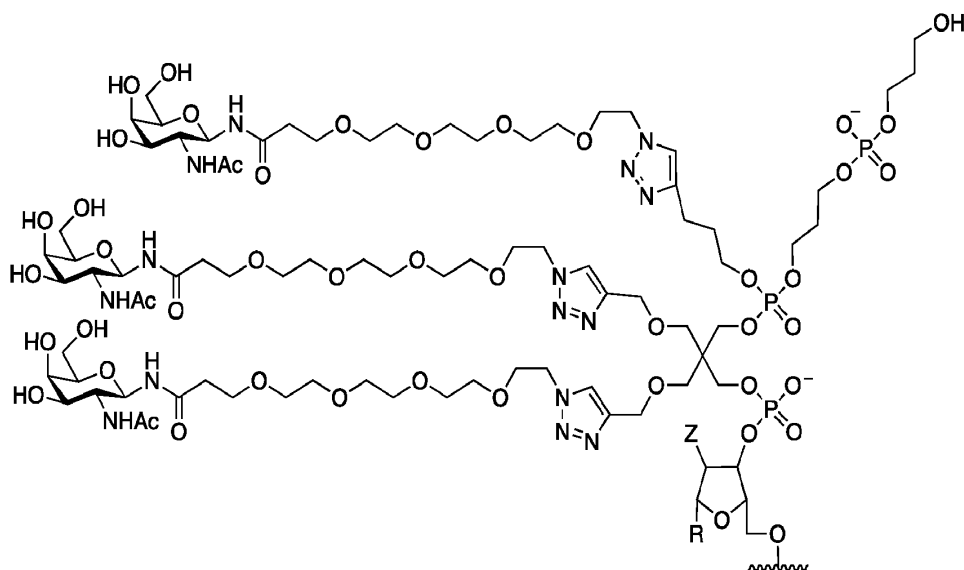
(V'''),

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.



(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.

[0157] In some instances, the 3' end of passenger/sense strand from Table 1, Table 3, Table 5, or Table 12 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 3, Table 5, or Table 12 is conjugated with X2-GalNAc (*see* Formula (V), (V''), or or (V''')). In some instances, a nucleic acid within passenger/sense strand (not at the 5' or 3' end) from Table 1, Table 3, Table 5, or Table 12 is conjugated with X2-GalNAc (*see* Formula (V)). In some instances, the 3' end of guide/antisense strand from Table 1, Table 3, Table 5, or Table 12 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 3, Table 5, or Table 12 is conjugated with X2-GalNAc (*see* Formula (V), (V''), or or (V''')). In some instances, a nucleic acid within guide/antisense strand (not at the 5' or 3' end) from Table 1, Table 3, Table 5, or Table 12 is conjugated with X2-GalNAc (*see* Formula (V)).

[0158] 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 HTL 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.

[0159] 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''', V''') through -LinkA-, as described herein.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

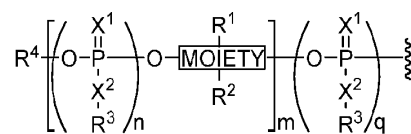
[0164] One or more cell penetrating peptides (e.g., from 1 to 6 or from 1 to 3) can be attached to a MOIETY or X2 in formula (V', V'', V''', V''', V''', V''', V''') through –LinkA–, as described herein.

[0165] 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.

[0166] 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

[0167] In some aspects, the polynucleic acid molecules described herein comprises a sense or antisense strand bonded to at least one group of formula (I)



(I)

or a salt thereof, or a stereoisomer thereof,

where

each X^1 is independently O or S;

each X^2 is independently O, S, NH, or a bond;

MOIETY is optionally substituted C_{2-10} alkane-tetrayl or a group $-M^1-M^2-M^3-$, wherein each M^1 and each M^3 is independently absent or optionally substituted C_{1-6} alkylene, and M^2 is optionally substituted C_{3-9} heterocycle-tetrayl, optionally substituted C_{6-10} arene-tetrayl, or optionally substituted C_{3-8} cycloalkane-tetrayl;

each R^1 and each R^2 is independently H, optionally substituted C_{1-16} alkyl, optionally substituted C_{2-16} heteroalkyl, a conjugation moiety, or $-\text{LinkA}(-T)_p$, provided that at least one R^1 or at least one R^2 is a conjugation moiety or $-\text{LinkA}(-T)_p$;

each R^3 is independently H, optionally substituted C_{1-16} alkyl, optionally substituted C_{2-16} heteroalkyl, optionally substituted C_{2-16} alkenyl, optionally substituted C_{2-16} alkynyl, optionally substituted $(C_{1-9}$ heterocyclyl)- C_{1-6} -alkyl, optionally substituted $(C_{6-10}$ aryl)- C_{1-6} -alkyl, optionally substituted $(C_{3-8}$ cycloalkyl)- C_{1-6} -alkyl, a conjugation moiety, or $-\text{LinkA}(-T)_p$;

R^4 is H, optionally substituted C_{1-6} alkyl, $-\text{LinkA}(-T)_p$, or $-\text{Sol}$;

each LinkA is independently a multivalent linker (e.g., including $-\text{C}(\text{O})-\text{N}(\text{H})-$ (e.g., at least one multivalent linker including $-\text{C}(\text{O})-\text{N}(\text{H})-$ 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;

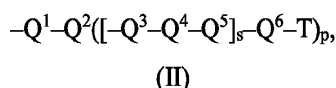
each p is independently an integer from 1 to 6; and

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.

[0168] 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).

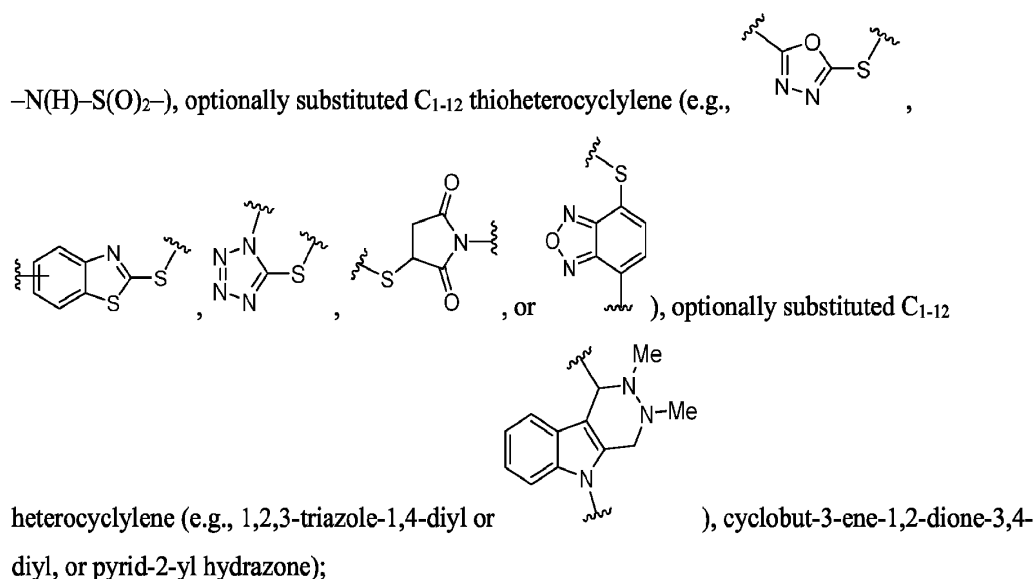
[0169] Group –LinkA(–T)_p in formula (I) may be prepared by a process described in the sections below. In some instances, –LinkA(–T)_p is of formula (II):



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;

Q¹ is a conjugation linker (e.g., [–Q³–Q⁴–Q⁵]_s–Q^C–, where Q^C is optionally substituted C₂₋₁₂ heteroalkylene (e.g., a heteroalkylene containing –C(O)–N(H)–, –N(H)–C(O)–, –S(O)₂–N(H)–, or



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

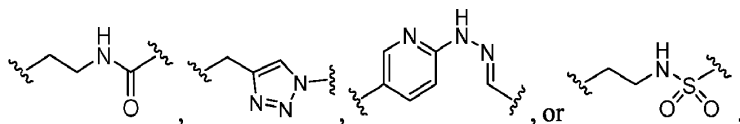
each R^a is independently H or an amino acid side chain;

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

[0170] 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.

[0171] 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.

[0172] In formula (II), Q^L may be $-O-Q^L-Q^C-$, where Q^L is optionally substituted C₂₋₁₂ heteroalkylene, optionally substituted C₁₋₁₂ 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 C₂₋₁₂ heteroalkylene or optionally substituted C₁₋₁₂ alkylene. In formula (II), Q^C may be:



[0173] In formula (II), Q² may be a linear group of formula $[-Q^3-Q^4-Q^5]_s-$, where Q³, Q⁴, and Q⁵ are as defined for formula (II). Alternatively, Q² 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 Q⁷ is independently optionally substituted C₁₋₆ alkane-triyl, optionally substituted C₁₋₆ alkane-tetrayl, optionally substituted C₂₋₆ heteroalkane-triyl, or optionally substituted C₂₋₆ heteroalkane-tetrayl;

where

p1 is 0 or 1;

p2 is 0, 1, 2, or 3;

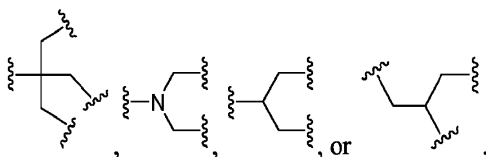
where,

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

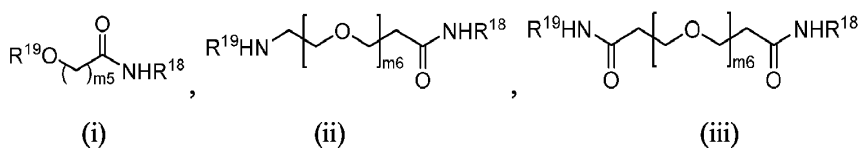
when p1 is 1, LinkA is a tetravalent, pentavalent, or hexavalent linker.

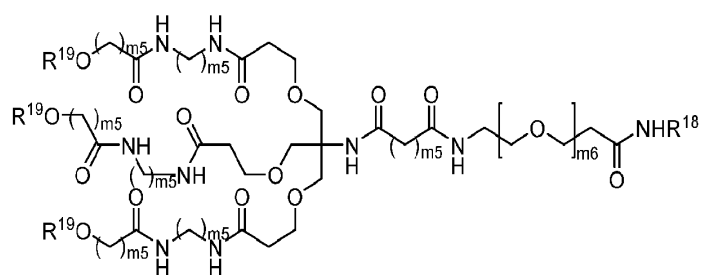
In certain aspects, p1 is 0.

In some aspects, Q⁷ is:

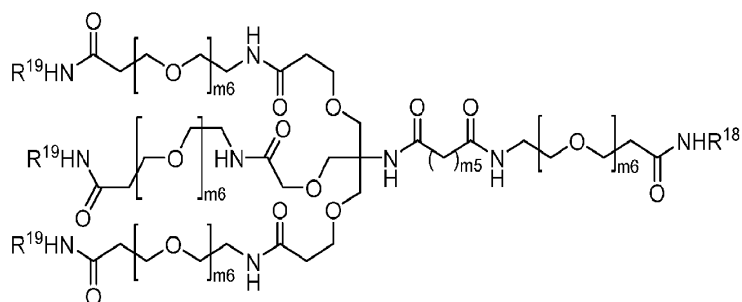


[0174] Compounds that may be used in the preparation of group $-\text{LinkA}(-T)_p$ in formula (I) are described herein as well as in WO 2015/188197. Non-limiting examples of $-\text{LinkA}$ include:

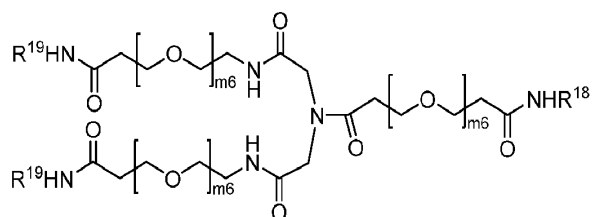




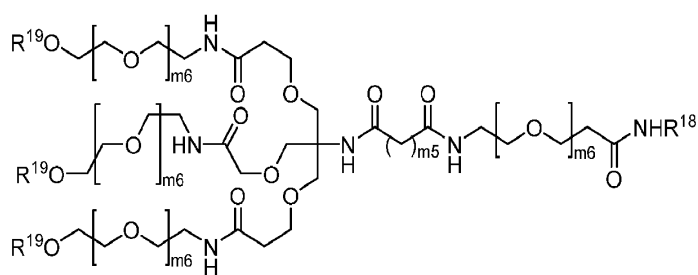
(iv)



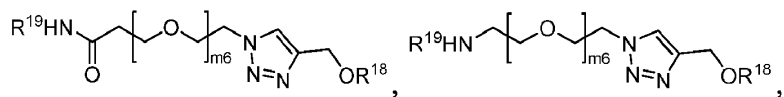
(v)



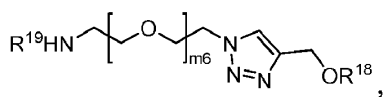
(vi)



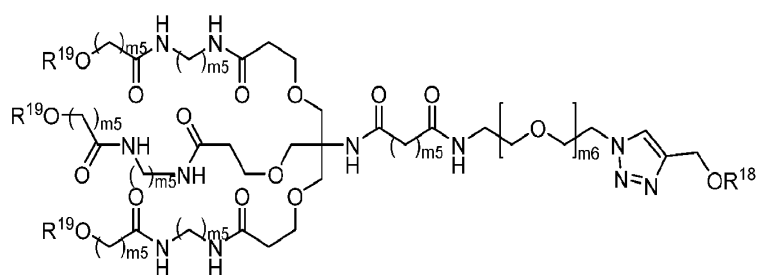
(vii)



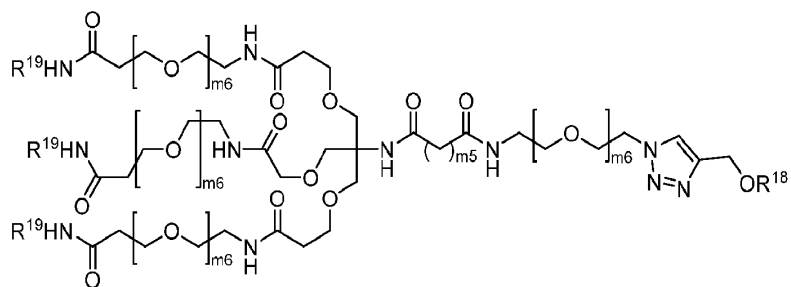
(viii)



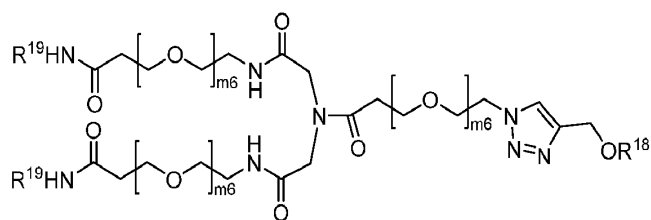
(ix)



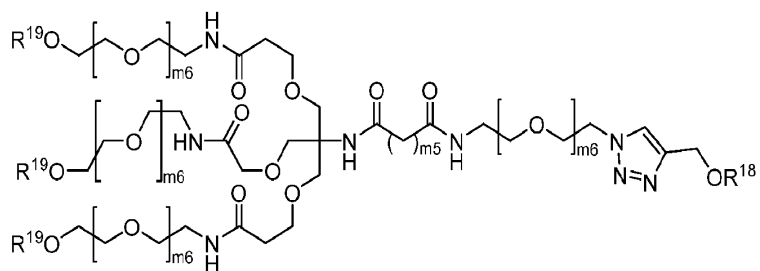
(x)



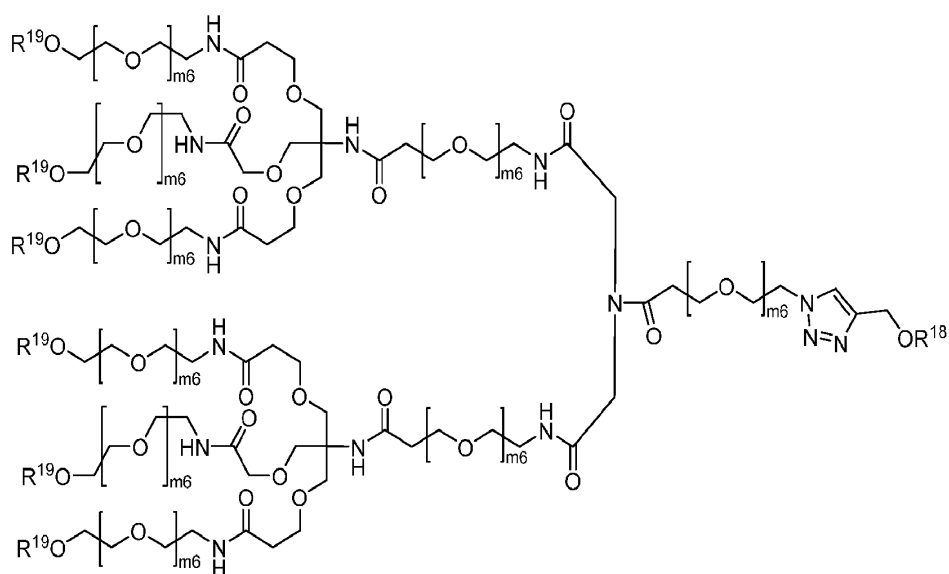
(xi)



(xii)

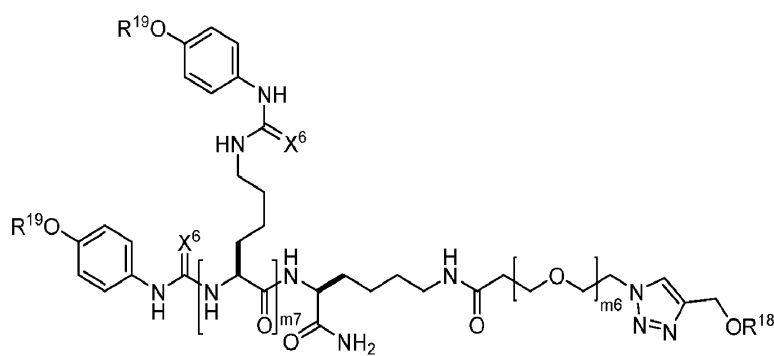


(xiii)



, and

(xiv)

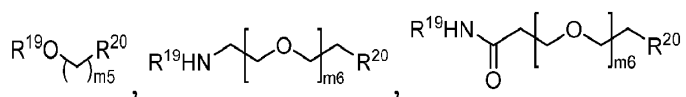


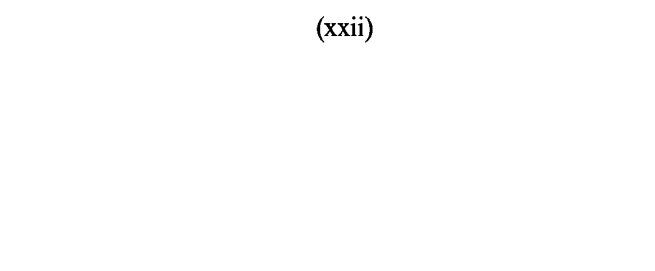
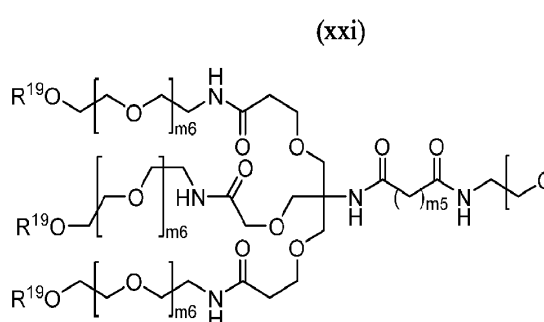
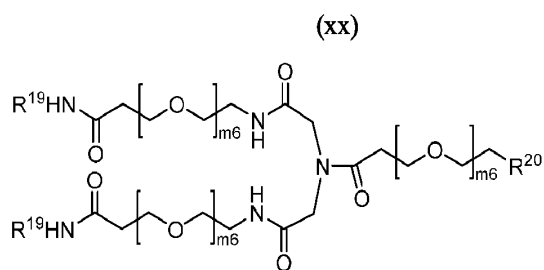
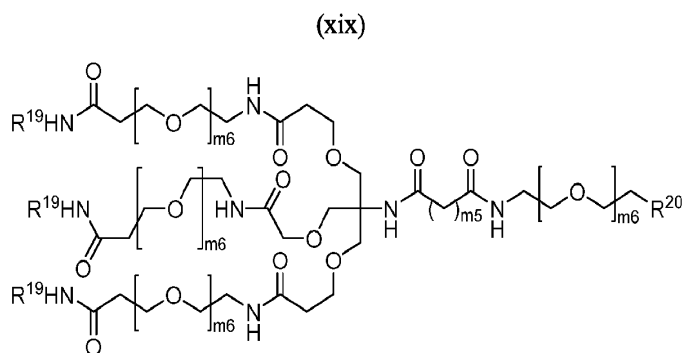
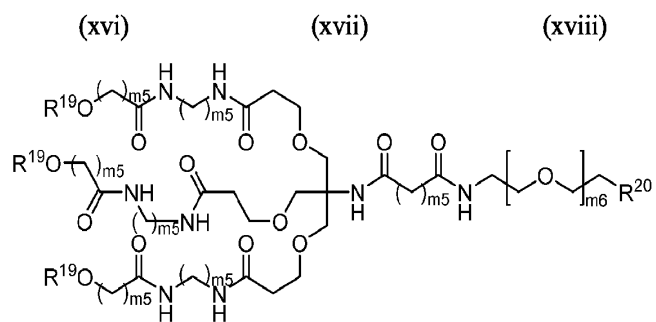
(xv)

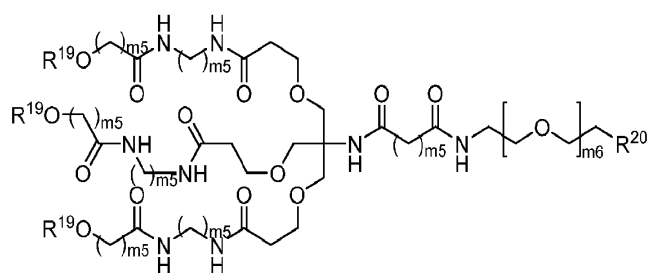
where

R¹⁸ is a bond to MOIETY,each R¹⁹ 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, andeach X⁶ is independently O or S.

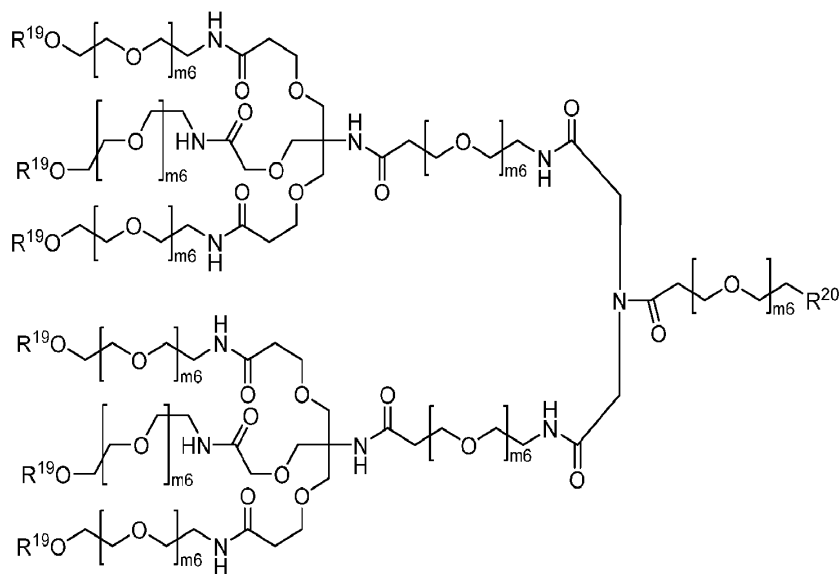
In formula (II), when the conjugation linker is of formula $[-Q^3-Q^4-Q^5]_s-Q^C-$, $-Q^2([Q^3-Q^4-Q^5]_s-Q^6-T)_p$ may be:





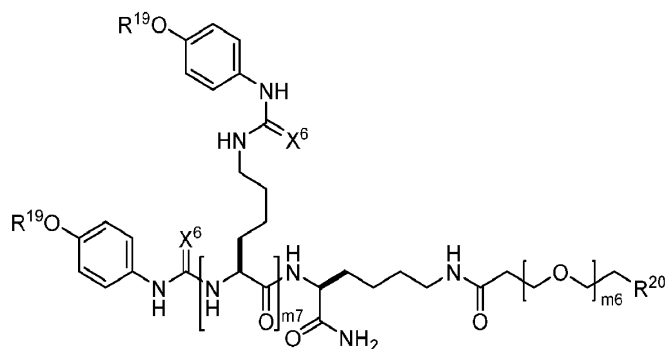


(xxiii)



, or

(xxiv)



(xxv)

where

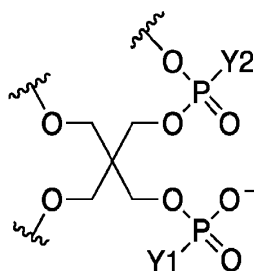
 R^{20} is a bond to Q^C in Q^1 ,each R^{19} is independently a bond to an auxiliary moiety,each $m5$ is independently an integer from 1 to 20,each $m6$ is independently an integer from 1 to 10,

m7 is an integer from 1 to 6, and

each X⁶ is independently O or S.

[0175] In some aspects, the linker described herein is cleavable. In some aspects, the linker described herein is non-cleavable.

[0176] In some aspects, the polynucleic acid molecule described herein comprises a sense or antisense strand bonded to at least one group of formula (IV),

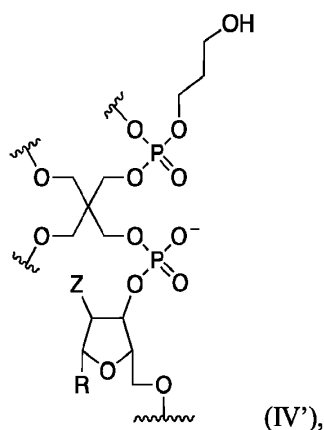


(IV),

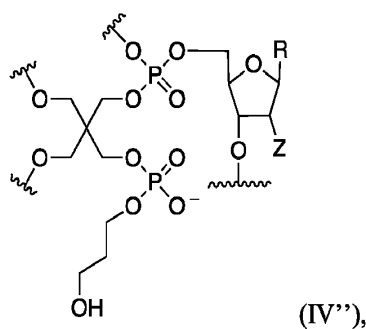
wherein at least one of Y1 or Y2 is a nucleotide from the polynucleic acid molecule.

[0177] 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 on the 5'-terminus or the last nucleotide on the 3'-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.

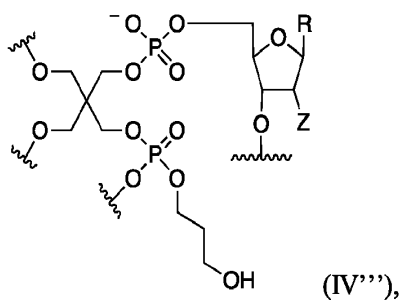
[0178] In some aspects, the targeting moiety described herein is conjugated to 3' end of the sense strand (e.g., formula (IV') or (IV''')). In some aspects, the targeting moiety described herein is conjugated to 5' end of the sense strand (e.g., formula (IV'') or (IV''')). In some aspects, the targeting 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''')).



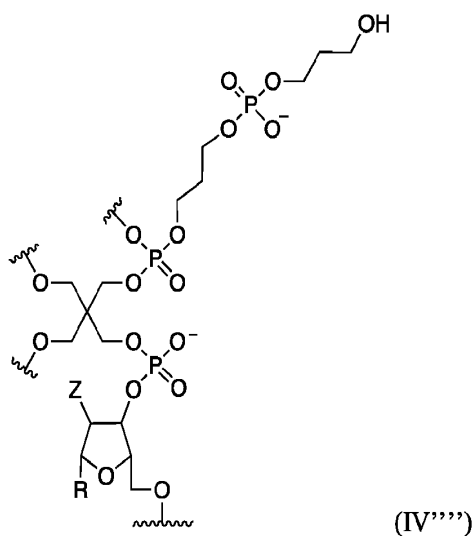
wherein Z in formula (IV') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (IV') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.



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.



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

[0179] 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.

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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.

[0184] 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.

[0185] 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 achieve. 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.

[0186] 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.

[0187] 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, dicaprinate, tricaprinate, monoolein, dilaurin, glyceryl 1-monocaprinate, 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.

[0188] 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.

[0189] 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.

[0190] 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).

[0191] 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

[0192] In some aspects, described herein is a method of modulating expression of *APOC3* 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 *APOC3* gene in the subject.

[0193] In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 10% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 20% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 30% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 40% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 50% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 60% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 70% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 80% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about or at least 90% compared to a negative control. In some aspects, the method described herein reduces expression of *APOC3* gene in a subject by about 100% compared to a negative control.

[0194] In some aspects, the method described herein achieves an IC₅₀ value of about 5nM. In some aspects, the method described herein achieves an IC₅₀ value of about 10nM. In some aspects, the method described herein achieves an IC₅₀ value of about 15nM. In some aspects, the method described herein achieves an IC₅₀ value of about 20nM. In some aspects, the method described herein achieves an IC₅₀ value of about 25nM. In some aspects, the method described herein achieves an IC₅₀ value of about 30nM. In some aspects, the method described herein achieves an IC₅₀ value of about 35nM. In some aspects, the method described herein achieves an IC₅₀ value of about 40nM. In some aspects, the method described herein achieves an IC₅₀ value of about 45nM. In some aspects, the method described herein achieves an IC₅₀ value of about 50nM. In some aspects, the method described herein achieves an IC₅₀ value of about 55nM. In some aspects, the method described herein achieves an IC₅₀ value of about 60nM. In some aspects, the method described herein achieves an IC₅₀ value of about 65nM. In some aspects, the

method described herein achieves an IC₅₀ value of about 70nM. In some aspects, the method described herein achieves an IC₅₀ value of about 75nM. In some aspects, the method described herein achieves an IC₅₀ value of about 80nM. In some aspects, the method described herein achieves an IC₅₀ value of about 85nM. In some aspects, the method described herein achieves an IC₅₀ value of about 90nM. In some aspects, the method described herein achieves an IC₅₀ value of about 95nM. In some aspects, the method described herein achieves an IC₅₀ value of about 100nM.

[0195] In some aspects, the method described herein achieves an IC₅₀ value of about 1 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 1.1 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 1.2 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 1.3 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 1.4 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 1.5 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 2 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 4 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 6 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 8 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 10 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 12 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 13 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 14 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 15 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 30 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 35 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 40 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 50 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 60 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 80 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 100 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 120 μ M. In some aspects, the method described herein achieves an IC₅₀ value of about 160 μ M.

[0196] In some aspects, described herein is a method of modulating triglyceride 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 expression of *APOC3* gene in the subject.

[0197] In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 10% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 20% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 30% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 40% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 50% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 60% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 70% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 80% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about or at least 90% compared to a negative control. In some aspects, the method described herein reduces triglyceride level in a subject by about 100% compared to a negative control.

[0198] In some aspects, the subject receiving the method described herein suffers from severe hypertriglyceridemia. In some specific case, the subject receiving the method described herein suffers from familial chylomicron syndrome (FCS). In other aspects, the subject receiving the method described herein suffers from high fasting triglycerides on restricted low-fat diet. In other aspects, the subject receiving the method described herein suffers from overweight or obese. In other aspects, the subject receiving the method described herein suffers from type 2 diabetes. In other aspects, the subject receiving the method described herein suffers from dyslipidaemia. In other aspects, the subject receiving the method described herein suffers a cardiovascular disease. In other aspects, the subject receiving the method described herein suffers from atherosclerosis. In other aspects, the subject receiving the method described herein suffers from stroke. In other aspects, the subject receiving the method described herein suffers from acute pancreatitis. In other aspects, the subject receiving the method described herein suffers from atherosclerotic cardiovascular disease. In other aspects, the subject receiving the method described herein suffers from atrial fibrillation. In other aspects, the subject receiving the method described herein suffers from myocardial infarction. In other aspects, the subject receiving the method described herein suffers from calcific aortic valve stenosis. In other aspects, the subject receiving the method

described herein suffers from cardiac arrest. In other aspects, the subject receiving the method described herein suffers from peripheral arterial disease.

EXEMPLARY EMBODIMENTS

[0199] Embodiment 1. A polynucleic acid molecule for modulating expression of apolipoprotein C3 (*APOC3*) gene, wherein the polynucleic acid molecule comprises a nucleic acid sequence that is at least 80%, at least 85%, at least 90% identical to a nucleic acid sequence in **Table 1**, **Table 3**, **Table 5**, or **Table 12**.

[0200] Embodiment 2. The polynucleic acid molecule of embodiment 1, wherein the polynucleic acid molecule comprises a nucleic acid sequence in Table 1, Table 3, Table 5, or Table 12.

[0201] 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.

[0202] 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: 217-324, 481-504, 541-546, and 575-585, with no more than 1, 2, 3, 4 mismatches.

[0203] Embodiment 5. The polynucleic acid molecule of embodiment 3, wherein the single-stranded nucleic acid molecule comprises a sequence that is at least 80%, at least 85%, at least 90%, at least 95% complementary to a nucleic acid sequence selected from SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585.

[0204] Embodiment 6. The polynucleic acid molecule of embodiment 3, wherein the single-stranded nucleic acid molecule comprises a 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: 1-108, 433-456, 529-534, and 553-563.

[0205] Embodiment 7. 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 identical to a nucleic acid sequence selected from SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563.

[0206] Embodiment 8. The polynucleic acid molecule of embodiment 1, wherein the polynucleic acid molecule is a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand.

[0207] Embodiment 9. The polynucleic acid molecule of embodiment 8, 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: 217-324, 481-504, 541-546, and 575-585.

[0208] Embodiment 10. The polynucleic acid molecule of embodiment 8, wherein the sense strand comprises a nucleic acid sequence that is at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 541-546 and 575-585.

[0209] Embodiment 11. The polynucleic acid molecule of any one of embodiments 8-10, 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: 1-108, 433-456, 529-534, and 553-563.

[0210] Embodiment 12. The polynucleic acid molecule of embodiment 11, wherein the antisense strand comprises a nucleic acid sequence that is at least 90%, at least 95% identical to a nucleic acid sequence selected from SEQ ID NOs: 529-534 and 553-563.

[0211] Embodiment 13. The polynucleic acid molecule of any one of embodiments 8-12, wherein the sense strand comprises a nucleic acid sequence comprising at least 14, 15, 16, 17, 18, 19, or 20 consecutive sequences of a nucleic acid sequence selected from SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 with no more than 1, 2, 3, or 4 mismatches.

[0212] Embodiment 14. The polynucleic acid molecule of any one of embodiments 8-13, 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: 1-108, 433-456, 529-534, and 553-563 with no more than 1, 2, 3, or 4 mismatches.

[0213] Embodiment 15. The polynucleic acid molecule of any one of embodiments 8-14, wherein the sense strand comprises a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563.

[0214] Embodiment 16. The polynucleic acid molecule of embodiment 15, wherein the sense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 541-546 and 575-585 and the antisense strand comprises a nucleic acid sequence selected from a nucleic acid sequence of SEQ ID NOs: 529-534 and 553-563.

[0215] Embodiment 17. The polynucleic acid molecule of any one of embodiments 1-16, wherein the polynucleic acid molecule comprises (1) a 2'-fluoro modified nucleotides; (2) a 2'-O-methyl modified nucleotides; (3) 2'-deoxy modified nucleotides, or (4) a modified internucleotide linkage.

[0216] Embodiment 18. The polynucleic acid molecule of any one of embodiments 1-17, wherein the polynucleic acid molecule comprise at least two consecutive modified internucleotide linkages at the 5' end.

[0217] Embodiment 19. The polynucleic acid molecule of any one of embodiments 8-18, wherein the antisense strand comprises at least two internucleotide linkages among 3 internucleotide linkages at the 3' end substituted with modified internucleotide linkages.

[0218] Embodiment 20. The polynucleic acid molecule of any one of embodiments 8-19, wherein the antisense strand comprises 5' - nNfnnnNfnNfNfnnnnNfnNfnnnnnnn-3', 5' - nNfnnnNfnnnnnnnNfnNfnnnnnnn-3', 5' - nNfnnnnNfnnnnNfnNfnnnnnnnn-3', 5' - nNfnnnnNfnnnnNfnNfnnnnnnnn-3', or 5' - nNfnnnnnnnnNfnNfNfnnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0219] Embodiment 21. The polynucleic acid molecule of any one of embodiments 8-20, wherein the sense strand comprises 5' - nnnnnnNfnNfnNfnnnnnnnnn-3', 5' - nnnnnnNfnNfNfNfnnnnnnnnn-3', 5' - nnnnnnnNfNfNfnnnnnnnnn-3', or 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 wherein "invN" stands for an inverted deoxy-nucleotide.

[0220] Embodiment 22. The polynucleic acid molecule of any one of embodiments 8-21, wherein the sense strand comprises 5' - NfnNfnNfnNfnNfnNfnNfnNfnNf-3', wherein the antisense strand comprises 5' - nNfnNfnNfnNfnNfnnnNfnNfnNfnNfn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0221] Embodiment 23. The polynucleic acid molecule of any one of embodiments 8-21, wherein the sense strand comprises 5' - nnnnnnNfnNfNfNfnnnnnnnnn -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.

[0222] Embodiment 24. The polynucleic acid molecule of any one of embodiments 8-21, wherein the sense strand comprises 5' - nnnnnnnNfnNfnnnnnnnnn -3', wherein the antisense strand comprises 5' - nNfnnnnnnnnNfnNfnnnnnnnn -3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0223] Embodiment 25. The polynucleic acid molecule of any one of embodiments 8-21, wherein the sense strand comprises 5' - nnnnnnNfnNfnNfnnnnnnnnn -3', wherein the antisense strand comprises 5' - nNfnnnnnnnnNfnNfnNfnnnnnnn -3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.

[0224] Embodiment 26. The polynucleic acid molecule of any one of embodiments 8-21, 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.

[0225] Embodiment 27. The polynucleic acid molecule of any one of embodiments 17-26, wherein the modified internucleotide linkage is a phosphorothioate internucleotide linkage.

[0226] Embodiment 28. The polynucleic acid molecule of any embodiment 27, wherein the modified internucleotide linkage comprises a stereochemically enriched phosphorothioate internucleotide linkage.

[0227] Embodiment 29. The polynucleic acid molecule of any one of embodiments 17-28, wherein the modified internucleotide linkage is an SP chiral internucleotide phosphorothioate linkage.

[0228] Embodiment 30. The polynucleic acid molecule of any one of embodiments 17-29, 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.

[0229] Embodiment 31. The polynucleic acid molecule of embodiment 30, wherein the stereochemically enriched phosphorothioate internucleotide linkages comprise both R- and S-isomers.

[0230] Embodiment 32. The polynucleic acid molecule of one of embodiments 30-31, wherein the 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.

[0231] Embodiment 33. The polynucleic acid molecule of any one of embodiments 1-32, wherein the polynucleic acid molecule comprises a hypoxanthine nucleobase-containing nucleoside substitution.

[0232] Embodiment 34. The polynucleic acid molecule of embodiment 33, wherein the hypoxanthine nucleobase-containing nucleoside substitution is an inosine substitution.

[0233] Embodiment 35. The polynucleic acid molecule of embodiment 34, wherein the inosine substitution is within a seed region of the antisense strand.

[0234] Embodiment 36. The polynucleic acid molecule of embodiment 34, wherein the inosine substitution is within 7 nucleotides from the 5' end of the antisense strand.

[0235] Embodiment 37. The polynucleic acid molecule of any one of embodiments 1-36, wherein the polynucleic acid molecule comprises an abasic substitution.

[0236] Embodiment 38. The polynucleic acid molecule of embodiment 37, wherein the abasic substitution is at the 5th or 7th nucleotide from the 5' end.

[0237] Embodiment 39. The polynucleic acid molecule of one of embodiments 17-38, wherein the cytotoxicity of the polynucleic acid molecule is decreased compared to unmodified polynucleic acid.

[0238] Embodiment 40. The polynucleic acid molecule of any one of embodiments 17-39, 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: 325-432, 505-528, 547-552, and 586-596.

[0239] Embodiment 41. The polynucleic acid molecule of any one of embodiments 17-39, 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: 109-216, 457-480, 535-540, and 564-574.

[0240] Embodiment 42. The polynucleic acid molecule of any one of embodiments 17-41, wherein the sense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596, and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574.

[0241] Embodiment 43. The polynucleic acid molecule of any one of embodiments 1-42, wherein the polynucleic acid molecule is 19-25 or 21-23 nucleotides in length.

[0242] Embodiment 44. A polynucleic acid molecule for modulating expression of apolipoprotein C3 (APOC3) gene, wherein polynucleic acid molecule comprises:

- (a) an antisense strand comprising the nucleotide sequence of UUUCAGGGAACUGAAGCCAUCGG (SEQ ID NO:529) and a sense strand comprising the nucleotide sequence of GAUGGCUUCAGUUCCCUGAAA (SEQ ID NO:541);
- (b) an antisense strand comprising the nucleotide sequence of UGAAUACUGUCCCUUUUAAGCAA (SEQ ID NO:530) and a sense strand comprising the nucleotide sequence of GCUUAAAAGGGACAGUAUUCA (SEQ ID NO:542);
- (c) an antisense strand comprising the nucleotide sequence of UAGAAUACUGUCCCUUUUAAGCA (SEQ ID NO:531) and a sense strand comprising the nucleotide sequence of CUUAAAAGGGACAGUAUUCUA (SEQ ID NO:543);
- (d) an antisense strand comprising the nucleotide sequence of UUGAGAAUACUGUCCCUUUUAAG (SEQ ID NO:532) and a sense strand comprising the nucleotide sequence of UAAAAGGGACAGUAUUCUCAA (SEQ ID NO:544);
- (e) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO:533) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO:545);

- (f) an antisense strand comprising the nucleotide sequence of UCACUGAGAAUACUGUCCCUUUU (SEQ ID NO:534) and a sense strand comprising the nucleotide sequence of AAGGGACAGUAUUCUCAGUGA (SEQ ID NO:546);
- (g) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 554) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 576);
- (h) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUCAA (SEQ ID NO: 555) and a sense strand comprising the nucleotide sequence of GAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 577);
- (i) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUGAA (SEQ ID NO: 556) and a sense strand comprising the nucleotide sequence of CAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 578);
- (j) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUGCAA (SEQ ID NO: 557) and a sense strand comprising the nucleotide sequence of GCAAGGGACAGUAUUCUCAGA (SEQ ID NO: 579);
- (k) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUCGAA (SEQ ID NO: 558) and a sense strand comprising the nucleotide sequence of CGAAGGGACAGUAUUCUCAGA (SEQ ID NO: 580);
- (l) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 559) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 581);
- (m) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUGAA (SEQ ID NO: 560) and a sense strand comprising the nucleotide sequence of CAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 582);
- (n) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 561) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 583);
- (o) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 562) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 584); or
- (p) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 563) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 585).

[0243] Embodiment 45. A polynucleic acid molecule for modulating expression of apolipoprotein C3 (APOC3) gene, wherein polynucleic acid molecule comprises:

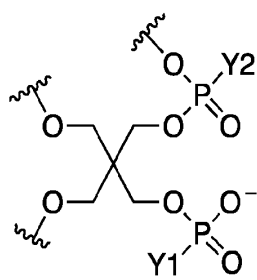
- (a) an antisense strand comprising the nucleotide sequence of usUfsucagGfgaacUfgAfaGfccaucsgsg (SEQ ID NO:535) and a sense strand comprising the nucleotide sequence of gsasuggcUfuCfaGfuucccugaaa (SEQ ID NO:547);
- (b) an antisense strand comprising the nucleotide sequence of usGfsaauaCfugucCfcUfuUfuaagcsasa (SEQ ID NO:536) and a sense strand comprising the nucleotide sequence of gscsuuaaAfaGfgGfacaguuuca (SEQ ID NO:548);
- (c) an antisense strand comprising the nucleotide sequence of usAfsgaauAfcuguCfcCfuUfuaagcsa (SEQ ID NO:537) and a sense strand comprising the nucleotide sequence of csusuaaaAfgGfgAfcaguuucua (SEQ ID NO:549);
- (d) an antisense strand comprising the nucleotide sequence of usUfsgagaAfuacuGfuCfcCfuuuuasag (SEQ ID NO:538) and a sense strand comprising the nucleotide sequence of usasaaagGfgAfcAfgauuucuaa (SEQ ID NO:550);
- (e) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuusasa (SEQ ID NO:539) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO:551);
- (f) an antisense strand comprising the nucleotide sequence of usCfsacugAfgaauAfcUfgUfcccususu (SEQ ID NO:540) and a sense strand comprising the nucleotide sequence of asasgggaCfaGfuAfuucucaguga (SEQ ID NO:552);
- (g) an antisense strand comprising the nucleotide sequence of vpusCfsugagAfaucUfgUfcCfcuuusasa (SEQ ID NO: 565) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 587);
- (h) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuusasa (SEQ ID NO: 566) and a sense strand comprising the nucleotide sequence of gsasaaggGfaCfaGfuauucucaga (SEQ ID NO: 588);
- (i) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuugsasa (SEQ ID NO: 567) and a sense strand comprising the nucleotide sequence of csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 589);
- (j) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuugcsasa (SEQ ID NO: 568) and a sense strand comprising the nucleotide sequence of gscsaaggGfaCfaGfuauucucaga (SEQ ID NO: 590);

- (k) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuucgsasa (SEQ ID NO: 569) and a sense strand comprising the nucleotide sequence of csgsaaggGfaCfaGfuauucucaga (SEQ ID NO: 591);
- (l) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuuusasa (SEQ ID NO: 570) and a sense strand comprising the nucleotide sequence of (invAb)asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 592);
- (m) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuugsasa (SEQ ID NO: 571) and a sense strand comprising the nucleotide sequence of (invAb)csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 593);
- (n) an antisense strand comprising the nucleotide sequence of usCfsugdAgdAauacUfgUfcCfcuuuusasa (SEQ ID NO: 572) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 594);
- (o) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfscCfcuuuusasa (SEQ ID NO: 573) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 595); or
- (p) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcsuuuusasa (SEQ ID NO: 574) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 596),
- wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “dA” refers to 2’-deoxyadenosine-3-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “dC” refers to 2’-deoxycytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “dG” refers to 2’-deoxyguanosine-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; “dT” refers to 2’-deoxythymidine-3’-phosphate; “s” refers to 3’-phosphorothioate, “(invAb)” refers to inverted abasic deoxyribonucleotide, and “vp” refers to 5’-vinylphosphonate modified nucleotide.

[0244] Embodiment 46. A polynucleic acid molecule conjugate for modulating expression of apolipoprotein C3 (APOC3) gene, wherein the polynucleic acid molecule conjugate comprises a polynucleic acid molecule of any one of embodiments 1-45 and an asialoglycoprotein receptor targeting moiety.

[0245] Embodiment 47. The polynucleic acid molecule conjugate of embodiment 46, wherein the polynucleic acid molecule and the asialoglycoprotein receptor targeting moiety is coupled via a linker.

[0246] Embodiment 48. The polynucleic acid molecule conjugate of embodiment 47, wherein the linker comprises formula (IV) below,



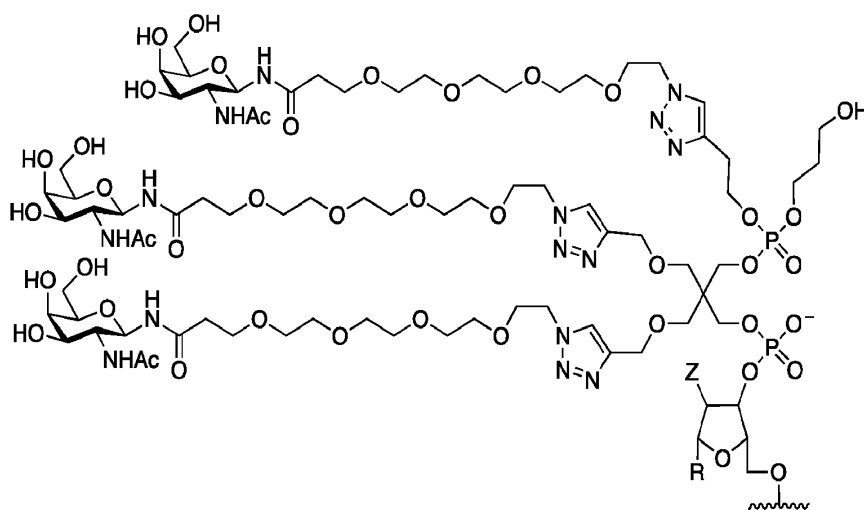
, wherein at least one of Y1 and Y2 is a nucleotide in the polynucleic acid molecule.

[0247] Embodiment 49. The polynucleic acid molecule conjugate of embodiment 48, wherein the Y1 is the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule.

[0248] Embodiment 50. The polynucleic acid molecule conjugate of embodiment 48, wherein the Y1 and Y2 are two consecutive nucleotides in the polynucleic acid molecule.

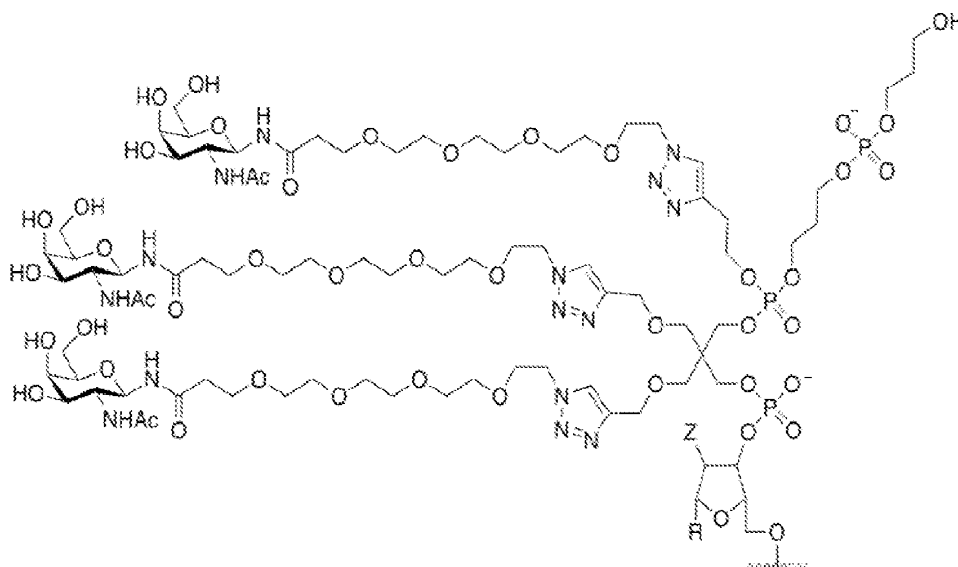
[0249] Embodiment 51. The polynucleic acid molecule conjugate of any one of embodiments 46-50, wherein the asialoglycoprotein receptor targeting moiety comprises N-Acetylgalactosamine (GalNAc) or galactose.

[0250] Embodiment 52. The polynucleic acid molecule conjugate of any one of embodiments 47-51, 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'):



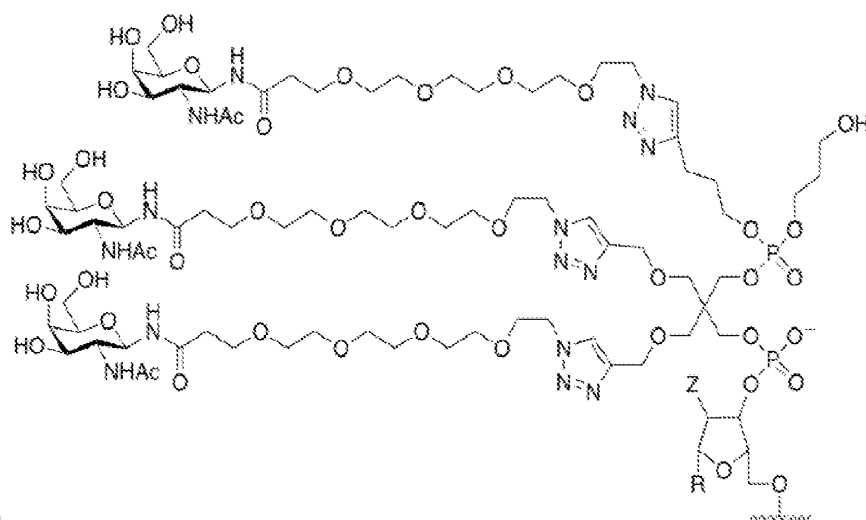
(V'), wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl, and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0251] Embodiment 53. The polynucleic acid molecule conjugate of any one of embodiments 47-51, 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'''):



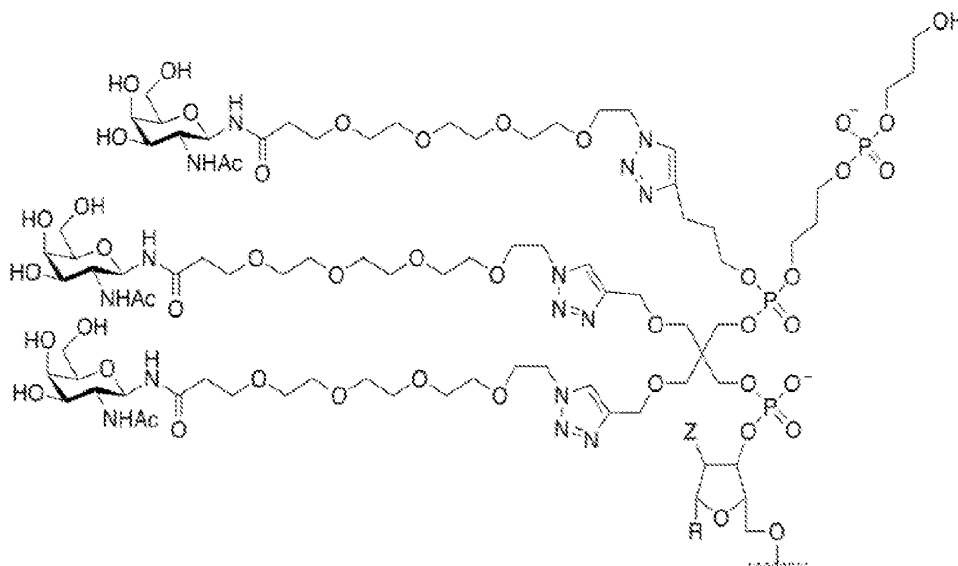
(V'''), wherein Z in formula (V''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others.

[0252] Embodiment 54. The polynucleic acid molecule conjugate of any one of embodiments 47-51, 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 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.

[0253] Embodiment 55. The polynucleic acid molecule conjugate of any one of embodiments 47-51, 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 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.

[0254] Embodiment 56. A pharmaceutical composition comprising a polynucleic acid molecule of any one of embodiments 1-45 or a polynucleic acid molecule conjugate of any one of embodiments 46-55, and a pharmaceutically acceptable excipient.

[0255] Embodiment 57. The pharmaceutical composition of embodiment 56, wherein the pharmaceutical composition is formulated as a nanoparticle formulation.

[0256] Embodiment 58. The pharmaceutical composition of embodiment 56 or embodiment 57, wherein the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.

[0257] Embodiment 59. A method of modulating expression of apolipoprotein C3 (APOC3) gene in a subject, comprising: administering to the subject a polynucleic acid molecule of any one of embodiments 1-45 or a polynucleic acid molecule conjugate of any one of embodiments 46-55, or a pharmaceutical composition of any one of embodiments 56-58, thereby modulating the expression of APOC3 gene in the subject.

[0258] Embodiment 60. A method of modulating triglyceride in a subject in need thereof, comprising: administering to the subject a polynucleic acid molecule of any one of embodiments 1-45 or a polynucleic acid molecule conjugate of any one of embodiments 46-55, or a pharmaceutical composition of any one of embodiments 56-58, thereby modulating triglyceride in the subject.

[0259] Embodiment 61. The method of embodiment 59 or 60, wherein the subject in need thereof suffers from cardiovascular disease or hypertriglyceridemia.

EXAMPLES

[0260] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein. For all of the sequences presented herein, oligonucleotide structure representation reads from left to right (5' to 3'). Monomer codes present in the oligonucleotide code are linked by 5'-3' phosphodiester bonds unless specified (succeeded by 3' internucleotide linkage reading left to right). Abbreviations of nucleotide monomers used in oligonucleotide structure representation are as follows. "A" stands for Adenosine-3'-phosphate; "a" stands for 2'-O-methyladenosine-3'-phosphate; "Af" stands for 2'-fluoroadenosine-3'-phosphate; "dA" stands for 2'-deoxyadenosine-3'-phosphate; "C" stands for Cytidine-3'-phosphate; "c" stands for 2'-O-methylcytidine-3'-phosphate; "Cf" stands for 2'-fluorocytidine-3'-phosphate; "dC" stands for 2'-deoxycytidine-3'-phosphate; "G" stands for Guanosine-3'-phosphate; "g" stands for 2'-O-methylguanosine-3'-phosphate; "Gf" stands for 2'-fluoroguanosine-3'-phosphate; "dG" stands for 2'-deoxyguanosine-3'-phosphate; "U" stands for Uridine-3'-phosphate; "u" stands for 2'-O-

methyluridine-3'-phosphate; "Uf" stands for 2'-fluorouridine-3'-phosphate; "dU" stands for 2'-deoxyuridine-3'-phosphate; "T" stands for 5-methyluridine-3'-phosphate; "t" stands for 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" stands for 2'-fluoro-5-methyluridine-3'-phosphate; "dT" stands for thymidine-3'-phosphate; and "s" stands for 3'-phosphorothioate.

Example 1 – *In vitro* efficacy of siRNAs targeting *APOC3*

[0261] A panel of siRNAs were generated (shown in **Table 1**), and the 3' end of each passenger/sense strand was conjugated with a triantennary GalNAc moiety (GalNAc-L96). The siRNA-GalNAc conjugates were evaluated *in vitro* in primary human hepatocytes.

[0262] Cryopreserved primary human hepatocytes (PHHs) were thawed and plated on collagen-coated 96-well plates at a density of 9×10^4 cells per well. Hepatocytes were treated by incubating with the siRNAs shown in **Table 1** with the 3' end of each passenger/sense strand conjugated with a triantennary GalNAc moiety in the absence of transfection reagents (free uptake) for 48 hours. Cells were treated with the siRNAs at concentrations of 10 μ M or 0.5 μ M. Untreated PHHs were used as a negative control. An siRNA targeting an unrelated gene (*Ahsa1*) was also used as a negative control. 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 (*e.g.*, human *GapDH*) using standard protocols. The *in-vitro* potency of the siRNAs are listed in **Table 2**.

Example 2 – Drug Response Curves for Selected *APOC3* siRNAs

[0263] A selected group of siRNAs targeting *APOC3* shown in **Table 3** were used, and the 3' end of each passenger/sense strand was conjugated with a triantennary GalNAc moiety (GalNAc-L96). The siRNA-GalNAc conjugates were evaluated at 10 different doses in primary human hepatocytes, using a similar experimental setup in Example 1. The corresponding drug response curves are depicted in **FIG. 1A** to **FIG. 1X**, and the IC_{50} and IC_{80} are specified in **Table 4**.

Example 3 – Testing *APOC3* siRNAs in Transgenic Mice

[0264] SRS-000231, SRS-000228, SRS-000229, or vehicle (1x PBS) were administered to *APOC3* transgenic mice (The Jackson Laboratory, B6;CBA-Tg(*APOC3*)3707/Bres/J, strain #006907) by subcutaneous injection (10 mL/kg). SRS-000231 and SRS-000228 treated groups were administered single doses at 10 mg/kg, 3 mg/kg, 1 mg/kg, or 0.3 mg/kg, and SRS-000229 treated groups were administered single doses at 10 mg/kg, 3 mg/kg, or 1 mg/kg. The 3' end of the passenger strand of each siRNA was conjugated with a triantennary GalNAc moiety (X2-GalNAc

as in Formula (V')). Plasma from all groups was collected on Days -4, 1, 7, 14, 21, 28, and 35. On day 35, liver tissue was collected for mRNA expression analysis.

[0265] Plasma total cholesterol levels, triglyceride levels, HDL-c levels, and LDL-c levels were measured. For each measurement and timepoint, the percentage relative to Day -4 values for each individual animal were determined, and the results were averaged. Group mean results along with standard deviations are listed in **Table 6**, **Table 7**, **Table 8**, and **Table 9**.

[0266] Plasma hAPOC3 protein levels on Days 1, 7, 14, 21, 28, and 35 were measured using an ELISA assay (Abcam, catalog #: ab154131). Due to insufficient residual sample for some animals and timepoints, results for each individual animal and timepoint were calculated as the percentage of circulating hAPOC3 protein relative to its group mean Day 1 value. The mean results along with standard deviation are listed in **Table 10**.

[0267] Total RNA from the day 35 liver samples was extracted, and levels of APOC3 mRNA were measured by RT-qPCR. Values of the SRS-000231, SRS-000228, and SRS-000229 treated animals were normalized to the PBS treated group APOC3 mRNA measurements. The mean results of percent remaining APOC3 mRNA for each group along with standard deviation are listed in **Table 11**.

[0268] SRS-000231, SRS-000228, and SRS-000229 each reduced plasma APOC3 (up to 88.5% in SRS-000228 treated group, for example) dose dependently across all timepoints. In addition, reductions in liver APOC3 mRNA (up to 96.7% in SRS-000231 treated group, for example) were observed at Day 35, relative to the control group. SRS-000231, SRS-000228, and SRS-000229 each reduced total cholesterol, triglycerides, and LDL-cholesterol throughout the study.

Example 4 – Testing *APOC3* siRNAs in Non-human Primates

[0269] Sequences of siRNAs used for the non-human primate study are specified in **Table 5** with the 3' end of each passenger/sense strand conjugated with a GalNAc via X2 (*see* Formula (V')). Male cynomolgus monkeys (n=4 per treatment group/siRNA) were administered a single 3 mg/kg subcutaneous injection of *APOC3* siRNA constructs SRS-000225 and SRS-000228 through SRS-000232 (as shown in **Table 5**). Blood samples were collected pre-dose (Day -1), and on days 3, 7, 10, 14, 21, 28, 35, and 42. APOC3 circulating protein levels in all serum samples were analyzed using an APOC3 immunoturbidimetric assay (Beijing Leadman Biochemistry, WGAB7031). Results were expressed as a percentage of circulating APOC3 protein remaining relative to the pre-dose timepoint, and are depicted in **FIG. 2**. To assess the depth of APOC3 mRNA silencing in liver tissue, ultrasound guided liver biopsies were collected pre-dose (day -1) and on days 21 and 42. At each timepoint, RT-qPCR was performed on all samples to measure APOC3 mRNA,

normalizing to reference genes ACTB, PPIA, and ARL1. APOC3 mRNA levels relative to the pre-dose timepoint are depicted in **FIGs. 3A-3C**.

[0270] Each siRNA reduced liver APOC3 mRNA relative to the pre-dose timepoint. For example, SRS-000231 reduced liver APOC3 mRNA by 90% on day 21 and day 42 when normalized to ACTB reference gene, and SRS-000228 reduced liver APOC3 mRNA by 89% on day 21 and 87% on day 42 when normalized to ACTB reference gene. Similar reductions were observed when normalized to ARL1 and PPIA.

[0271] Further, each siRNA reduced serum APOC3 relative to the pre-dose timepoint. For example, SRS-000231 reduced serum APOC3 by 64% on day 21 and 54% on day 42.

Example 5 – Testing *APOC3* siRNAs in transgenic mice

[0272] Sequences of siRNAs listed in **Table 12**, or vehicle (1x PBS) were administered to APOC3 transgenic mice (The Jackson Laboratory, B6;CBA-Tg(APOC3)3707/Bres/J, strain #006907) at a single 0.5 mg/kg dose by subcutaneous injection (10 mL/kg). The 3' end of the passenger strand of each siRNA was conjugated with a triantennary GalNAc moiety (X2-GalNAc as in Formula (V')). Plasma from all groups was collected on Days -4, 1, 7, 14, 21, 28, 35, 42, 49, and 56. On day 56, liver tissue was collected for mRNA expression analysis.

[0273] Plasma total cholesterol levels, triglyceride levels, HDL-c levels, and LDL-c levels were measured. For each measurement and timepoint, the percentage relative to Day 1 values for each individual animal were determined, and the results were averaged. Group mean results along with standard deviations are listed in **Table 13**, **Table 14**, **Table 15**, and **Table 16**.

[0274] Plasma hAPOC3 protein levels on Days 1, 7, 14, 21, 28, 35, 49, and 56 were measured using an ELISA assay (Abcam, catalog #: ab154131). Due to insufficient residual sample for some animals and timepoints, results for each individual animal and timepoint were calculated as the percentage of circulating hAPOC3 protein relative to its group mean Day 1 value. The mean results along with standard deviation are listed in **Table 17**.

[0275] Total RNA from the day 56 liver samples was extracted, and levels of APOC3 mRNA were measured by RT-qPCR. Values of the siRNA treated animals were normalized to the PBS treated group APOC3 mRNA measurements. The mean results of APOC3 mRNA expression relative to the vehicle control group along with standard deviation are listed in **Table 18**.

[0276] Following a single 0.5 mg/kg dose, all siRNAs reduced plasma APOC3 levels significantly. For example, the range of plasma APOC3 reduction following treatment of SRS-000231 was 69.6% to 89% from day 7 through day 56. Total cholesterol, triglycerides, and LDL-cholesterol were also reduced following treatment of each siRNA. For example, by Day 7, SRS-000231

reduced total cholesterol, triglycerides, and LDL-cholesterol by 70.1%, 90%, and 95.2%, respectively, and levels remained low through day 56. In addition, liver APOC3 mRNA remained significantly reduced at day 56 (end of study). For example, SRS-000231 reduced liver APOC3 mRNA by 74% . Exemplary siRNAs SRS-001860, SRS-001861, SRS-001862, and SRS-001863 reduced liver APOC3 mRNA by 93%, 95%, 97%, and 94%, respectively.

[0277] 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 1. Sequence Information for siRNAs Evaluated *in vitro*

Duplex ID	Target Position	SEQ ID NO.	Guide/Antisense Structure Code (5'-3')	SEQ ID NO.	Guide/Antisense Base Sequence (5'-3')	SEQ ID NO.	Passenger/Sense Structure Code (5'-3')	SEQ ID NO.	Passenger/Sense Base Sequence (5'-3')
SRS-000662	31	109	usCbaagCfaccuChfuUfcuaggaag	1	UCAUGGCACCUUCUUGUCCUGGAG	325	cscsaggaAfcAfgAfgugccauga	217	CCAAGAAACAGAGGUGCCAUGA
SRS-000663	43	110	usUfaaccCfaggcUfgChfUfgcacacu	2	UUACCCGGGGUGCAUGGCAACCU	326	gaugacaUfgChfGfcccggguua	218	GUGCCAUGCAGCCCCCGGUAA
SRS-000664	44	111	usGfsuaccCfaggcChfCfcAfuaggcacsc	3	UGUACCCGGGGUGCAUGGCACC	327	usgsccauCfcAfgCfcccggguaca	219	UGCCAUGCAGCCCCCGGUACA
SRS-000665	45	112	usAfgsuacCfaggcGfcUfgCfauggcacsc	4	UAGUACCCGGGGUGCAUUGCAC	328	gscscaugCfagGfcCfcccggguaca	220	GCCAUGCAGCCCCCGGUACAUA
SRS-000666	49	113	usAfaaggaCfhaaccCfpgCfpgcasug	5	UAAAGGAGUACCCGGGGUGCAUG	329	usgsacgcCfcCfpgGfpuacuucua	221	UGCAGCCCCGGGUACUCCUUA
SRS-000667	51	114	usAfscaagCfaguaCfcCfpgGfpgcscsa	6	UACAAGGAGUACCCGGGGUGCA	330	csasgcgcCfpgGfpuafacuucua	222	CAGCCCCGGGUACUCCUUGUA
SRS-000668	52	115	usAfscaacCfagguAfcCfcGfpgcscsc	7	UACAAGGAGUACCCGGGGUGC	331	asgsccgcGfpgGfpuafacuucua	223	AGCCCCGGGUACUCCUUGUA
SRS-000669	54	116	usAfscaacAfggaCfhaAfcCfpgcscsc	8	UACAACAAGGAGUACCCGGGGCU	332	cscsaggaCfhaAfcUfcuugua	224	CCCCGGGUACUCCUUGUUGUA
SRS-000670	55	117	usAfscaacCfhaagAfgUfaCfpgcscsc	9	UACAACAAGGAGUACCCGGGGC	333	cscsaggaCfhaAfcUfcuugua	225	CCCCGGGUACUCCUUGUUGUA
SRS-000671	57	118	usGfscaacAfaaaCfpgAfgUfaccggsg	10	UGCAACAACAAGGAGUACCCGGG	334	csaggaCfhaAfcUfcuugua	226	CGGUACUCCUUGUUGUUGCA
SRS-000672	58	119	usGfscaacCfhaaAfgCfhaGfhaaccsg	11	UGCAACAACAAGGAGUACCCGG	335	gsaggaCfhaAfcUfcuugua	227	GGUACUCCUUGUUGUUGCCA
SRS-000673	59	120	usGfscaacAfaaaCfpgAfgUfaccsg	12	UGGGCAACAACAAGGAGUACCCG	336	gsaggaCfhaAfcUfcuugua	228	GUACUCCUUGUUGUUGCCA
SRS-000674	60	121	usAfgggcAfaaaCfhaAfgGfhaaccsc	13	UAGGGCAACAACAAGGAGUACCC	337	gsuacgcCfhaAfgUfcuugua	229	GUACUCCUUGUUGUUGCCA
SRS-000675	64	122	usCbaagCfaggcAfcAfaCfaaggaagau	14	UCAGGAGGGCAACAACAAGGAGU	338	usccuugCfhaAfgUfcuugua	230	UCCUUGUUGUUGUUGCCA
SRS-000676	66	123	usGfscaagCfaggcCfhaAfcAfaaaagga	15	UGCCAGGAGGGCAACAACAAGGA	339	csuugauCfhaAfgUfcuugua	231	CUUGUUGUUGUUGUUGCCA
SRS-000677	88	124	usAfgcucCfaggcCfhaAfgCfaggaag	16	UAGCUCGGGCAGAGGCCAGGC	340	usccuugCfhaAfgUfcuugua	232	UCCUUGUUGUUGUUGCCA
SRS-000678	90	125	usGfsaagCfaggcCfhaAfgCfaggaag	17	UGAAGCUCGGGCAGAGGCCAGGA	341	csuugauCfhaAfgUfcuugua	233	CUGGCCUUGUUGUUGCCA
SRS-000679	92	126	usCfsuagCfaggaCfhaAfgCfaggaag	18	UCUGAAGCUCGGGCAGAGGCCAG	342	gsaggaCfhaAfgUfcuugua	234	GGCCUUGUUGUUGUUGCCA
SRS-000680	93	127	usUfscuagAfgcucCfhaAfgCfaggaag	19	UUCUGAAGCUCGGGCAGAGGCCA	343	gsccuagCfhaAfgUfcuugua	235	GCCUUGUUGUUGUUGCCA
SRS-000681	95	128	usCfsuagCfaggaCfhaAfgCfaggaag	20	UCCUCUGAAGCUCGGGCAGAGGC	344	csuugauCfhaAfgUfcuugua	236	CUUGUUGUUGUUGUUGCCA
SRS-000682	97	129	usGfsuagCfaggaCfhaAfgCfaggaag	21	UGGCCUCUGAAGCUCGGGCAGAG	345	csuugauCfhaAfgUfcuugua	237	CUGGCCUUGUUGUUGCCA
SRS-000683	98	130	usCfsuagCfaggaCfhaAfgCfaggaag	22	UCGGCUCUGAAGCUCGGGCAGAG	346	usgsccgcAfgCfhaAfgCfaggaag	238	UGGCCUUGUUGUUGUUGCCA
SRS-000684	99	131	usUfscuagCfaggaCfhaAfgCfaggaag	23	UUCGGCUCUGAAGCUCGGGCAG	347	gsccuagCfhaAfgUfcuugua	239	GCCUUGUUGUUGUUGCCA

[illegible]

Duplex ID	Target Position	SEQ ID NO.	Guide/Antisense Structure Code (5'-3')	SEQ ID NO.	Guide/Antisense Base Sequence (5'-3')	SEQ ID NO.	Passenger/Sense Structure Code (5'-3')	SEQ ID NO.	Passenger/Sense Base Sequence (5'-3')
SRS-000712	235	159	usGfagaacUfgaagCfcaAfuCfagacacsc	51	UGGAA CUGAAGCCAUCCGUCACC	375	usgsaacgAfuGfGfChucacgucua	267	UGACCGAUGGCUUCA GUUCCA
SRS-000713	240	160	usUfucagCfgaacUfgAfuGfcaucaggg	52	UUUCAGGGAACUGAAGCCAUCCG	376	gsasuggeUfuCfcaGfhuccucgaaa	268	GAUGGUUUCAGUUCUCCUGAAA
SRS-000714	248	161	usA fsguagUfennuChfGfGfGfcaucgsaa	53	UAGUAGUCUUUUCAGGGAACUGAA	377	csasguncCfcaUfgAfaagacuaa	269	CAGUUCUCCUGAAAGACUACUA
SRS-000715	257	162	usCfsggugChucacGfuAfgUfennucsaag	54	UGGGUGUCCACGUAAGUCUUUCAG	378	gsasagaCfuAfcUfgfagacacgaa	270	GAAAGACUACUGGAGCACCGGA
SRS-000716	259	163	usA fcaaggUfgucCfcaGfuAfgucmusc	55	UAAACGGUGUCCAGUAGUCUUUC	379	asasgacuAfcUfgGfagacacguaa	271	AAGACUACUGGAGCACCGUUA
SRS-000717	260	164	usUfcaagCfhuCfcaAfgUfagucuuuu	56	UUAACGGUGUCCAGUAGUCUUU	380	asasgacuAfcUfgGfagacacguaa	272	AGACUACUGGAGCACCGUUA
SRS-000718	261	165	usUfcaagCfhuCfcaAfgUfagucuuuu	57	UUUAAACGGUGUCCAGUAGUCUU	381	gsasgacuAfcUfgGfagacacguaa	273	GACUACUGGAGCACCGUUA
SRS-000719	262	166	usCfcaagCfhuCfcaAfgUfagucuuuu	58	UCUUAAACGGUGUCCAGUAGUCU	382	asasgacuAfcUfgGfagacacguaa	274	ACUACUGGAGCACCGUUA
SRS-000720	263	167	usCfcaagCfhuCfcaAfgUfagucuuuu	59	UCCUUAAACGGUGUCCAGUAGUC	383	csasgacuAfcUfgGfagacacguaa	275	CUACUGGAGCACCGUUA
SRS-000721	264	168	usUfcaagCfhuCfcaAfgUfagucuuuu	60	UUUUAAACGGUGUCCAGUAGUCU	384	usasgacuAfcUfgGfagacacguaa	276	UACUGGAGCACCGUUA
SRS-000722	265	169	usUfcaagCfhuCfcaAfgUfagucuuuu	61	UGUCCUUAAACGGUGUCCAGUAG	385	asasgacuAfcUfgGfagacacguaa	277	ACUGGAGCACCGUUA
SRS-000723	266	170	usUfcaagCfhuCfcaAfgUfagucuuuu	62	UUGUCCUUAAACGGUGUCCAGUAG	386	csasgacuAfcUfgGfagacacguaa	278	CUUGGAGCACCGUUA
SRS-000724	267	171	usUfcaagCfhuCfcaAfgUfagucuuuu	63	UUUUGUCCUUAAACGGUGUCCAGU	387	usgsagacAfcCfGfUfuaagacaaa	279	UGGAGCACCGUUA
SRS-000725	268	172	usCfcaagCfhuCfcaAfgUfagucuuuu	64	UCUUGUCCUUAAACGGUGUCCAG	388	gsasagacAfcCfGfUfuaagacaaa	280	GGAGCACCGUUA
SRS-000726	269	173	usA fcaagUfennuAfcUfgGfagacacgaa	65	UACUUGUCCUUAAACGGUGUCCAG	389	gsasgacuAfcUfgGfagacacguaa	281	GACACCGUUA
SRS-000727	271	174	usGfcaagUfennuAfcUfgGfagacacgaa	66	UGAACUUGUCCUUAAACGGUGUCC	390	gsasgacuAfcUfgGfagacacguaa	282	GCACCGUUA
SRS-000728	272	175	usA fgaagUfennuAfcUfgGfagacacgaa	67	UAGAACUUGUCCUUAAACGGUGUCC	391	csasgacuAfcUfgGfagacacguaa	283	CACCGUUA
SRS-000729	274	176	usA fgaagUfennuAfcUfgGfagacacgaa	68	UAGAGAACUUGUCCUUAAACGGUG	392	csasgacuAfcUfgGfagacacguaa	284	CGUUA
SRS-000730	275	177	usCfcaagCfhuCfcaAfgUfagucuuuu	69	UCAGAGAACUUGUCCUUAAACGGU	393	csasgacuAfcUfgGfagacacguaa	285	CGUUA
SRS-000731	279	178	usA fcaagUfennuAfcUfgGfagacacgaa	70	UAAUCACAGAGAACUUGUCCUUAA	394	asasgacuAfcUfgGfagacacguaa	286	AAGGACUUA
SRS-000732	294	179	usGfcaagUfennuAfcUfgGfagacacgaa	71	UGGGUCCAAAUCCAGAGAACUUCAG	395	gsasgacuAfcUfgGfagacacguaa	287	GAGUUCUGGGAU
SRS-000733	312	180	usCfcaagUfennuAfcUfgGfagacacgaa	72	UGAAGUUGUCCUAGUCCUAGGCU	396	csasgacuAfcUfgGfagacacguaa	288	CCUGGAGUCCU
SRS-000734	318	181	usA fcaagUfennuAfcUfgGfagacacgaa	73	UACGGUGAGAACUUGUCCUAGGCU	397	gsasgacuAfcUfgGfagacacguaa	289	GUCAGACUUA
SRS-000735	320	182	usCfcaagUfennuAfcUfgGfagacacgaa	74	UCCAGGUGAGAACUUGUCCUAGGCU	398	csasgacuAfcUfgGfagacacguaa	290	CAGACUUA
SRS-000736	339	183	usGfcaagUfennuAfcUfgGfagacacgaa	75	UGUUAUGAGGUGUCCUAGGCU	399	gsasgacuAfcUfgGfagacacguaa	291	GCUGGAGUCCU
SRS-000737	340	184	usGfcaagUfennuAfcUfgGfagacacgaa	76	UGGUUAUGAGGUGUCCUAGGCU	400	csasgacuAfcUfgGfagacacguaa	292	CUUGGAGUCCU
SRS-000738	342	185	usGfcaagUfennuAfcUfgGfagacacgaa	77	UGGGUUAUGAGGUGUCCUAGGCU	401	gsasgacuAfcUfgGfagacacguaa	293	GCCUGAGUCCU

Duplex ID	Target Position	SEQ ID NO.	Guide/Antisense Structure Code (5'-3')	SEQ ID NO.	Guide/Antisense Base Sequence (5'-3')	SRQ ID NO.	Passenger/Sense Structure Code (5'-3')	SEQ ID NO.	Passenger/Sense Base Sequence (5'-3')
SRS-000739	343	186	usUfsgagUfuaugAfgGfufhacgagcsaa	78	UUGGGGUUUGAGGUCUCAGGCA	402	csusugAfgCfufhauuacccaa	294	CCUGAGACCUCAUAUACCCAA
SRS-000740	346	187	usAfsicungGfguaUfufhGfufgucucsaag	79	UACUUGGGGUUUGAGGUCUCAG	403	gsasgacUfufAfaUfaccuccaagua	295	GAGACCUCAUAUACCCAAAGUA
SRS-000741	347	188	usGfhaucmGfgagUafufgAfgucucsa	80	UGACUUGGGGUUUGAGGUCUCA	404	agsaucCfhaAfaUfaccucca	296	AGACCUCAUAUACCCAAAGUCA
SRS-000742	348	189	usGfhaucmUfsgagUfufhGfagucucsc	81	UGGACUUGGGGUUUGAGGUCUC	405	gsasuccAfaUfufaccucca	297	GACCUCAUAUACCCAAAGUCA
SRS-000743	389	190	usGfhaucmUfsgagUfufhGfagucucsc	82	UGAUUGCAGGACCCAAAGGAGCUC	406	gsaucUfufgGfufgUfucugcauca	298	GCUCUUGGUGUCUGCAAUCA
SRS-000744	391	191	usGfhaucmUfsgagUfufhGfagucucsc	83	UGAGAUUGCAGGACCCAAAGGAGC	407	usaucmGfufgUfufhGfagucuca	299	UCCUUGGUGUCUGCAAUUCUCA
SRS-000745	392	192	usGfsgagUfufgagUfufhGfagucucsc	84	UGGAGAUUGCAGGACCCAAAGGAG	408	csusugUfufhGfufgUfucucuca	300	CCUUGGUGUCUGCAAUUCUCA
SRS-000746	393	193	usUfsgagUfufgagUfufhGfagucucsc	85	UUGGAGAUUGCAGGACCCAAAGGA	409	csusugUfufhGfufgUfucucuca	301	CUUGGUGUCUGCAAUUCUCA
SRS-000747	394	194	usCfsgagUfufgagUfufhGfagucucsc	86	UCUGGAGAUUGCAGGACCCAAAGG	410	usugagUfufhGfufgUfucucuca	302	UUGGUGUCUGCAAUUCUCA
SRS-000748	395	195	usCfsgagUfufgagUfufhGfagucucsc	87	UCCUGGAGAUUGCAGGACCCAAAG	411	usugagUfufhGfufgUfucucuca	303	UGGUGUCUGCAAUUCUCA
SRS-000749	396	196	usCfsgagUfufgagUfufhGfagucucsc	88	UCCUGGAGAUUGCAGGACCCAAAG	412	gsugagUfufhGfufgUfucucuca	304	GGGUGUCUGCAAUUCUCA
SRS-000750	397	197	usGfsgagUfufgagUfufhGfagucucsc	89	UGGUGGAGAUUGCAGGACCCAAAG	413	gsugagUfufhGfufgUfucucuca	305	GGGUGUCUGCAAUUCUCA
SRS-000751	422	198	usCfsgagUfufgagUfufhGfagucucsc	90	UCCUGGAGAUUGCAGGACCCAAAG	414	csusugUfufhGfufgUfucucuca	306	CUUGGUGUCUGCAAUUCUCA
SRS-000752	424	199	usGfsgagUfufgagUfufhGfagucucsc	91	UGGUGGAGAUUGCAGGACCCAAAG	415	gsugagUfufhGfufgUfucucuca	307	GUUGGUGUCUGCAAUUCUCA
SRS-000753	431	200	usGfsgagUfufgagUfufhGfagucucsc	92	UGGUGGAGAUUGCAGGACCCAAAG	416	gsugagUfufhGfufgUfucucuca	308	GGGUGGAGAUUGCAGGACCA
SRS-000754	433	201	usGfsgagUfufgagUfufhGfagucucsc	93	UGGUGGAGAUUGCAGGACCCAAAG	417	usugagUfufhGfufgUfucucuca	309	UUUUUUUUUUUUUUUUUUUU
SRS-000755	434	202	usUfsgagUfufgagUfufhGfagucucsc	94	UUGGAGAUUGCAGGACCCAAAG	418	usugagUfufhGfufgUfucucuca	310	UUUUUUUUUUUUUUUUUUUU
SRS-000756	435	203	usCfsgagUfufgagUfufhGfagucucsc	95	UCUGGAGAUUGCAGGACCCAAAG	419	asugagUfufhGfufgUfucucuca	311	UUUUUUUUUUUUUUUUUUUU
SRS-000757	436	204	usAfsicagUfufgagUfufhGfagucucsc	96	UACUGGAGAUUGCAGGACCCAAAG	420	asugagUfufhGfufgUfucucuca	312	UUUUUUUUUUUUUUUUUUUU
SRS-000758	437	205	usCfsgagUfufgagUfufhGfagucucsc	97	UACUGGAGAUUGCAGGACCCAAAG	421	asugagUfufhGfufgUfucucuca	313	UUUUUUUUUUUUUUUUUUUU
SRS-000759	438	206	usGfsgagUfufgagUfufhGfagucucsc	98	UCCUGGAGAUUGCAGGACCCAAAG	422	asugagUfufhGfufgUfucucuca	314	UUUUUUUUUUUUUUUUUUUU
SRS-000760	441	207	usAfsicagUfufgagUfufhGfagucucsc	99	UAGGAGAUUGCAGGACCCAAAG	423	gsugagUfufhGfufgUfucucuca	315	UUUUUUUUUUUUUUUUUUUU
SRS-000761	442	208	usGfsgagUfufgagUfufhGfagucucsc	100	UGGAGAUUGCAGGACCCAAAG	424	asugagUfufhGfufgUfucucuca	316	UUUUUUUUUUUUUUUUUUUU
SRS-000762	446	209	usGfsgagUfufgagUfufhGfagucucsc	101	UGGAGAUUGCAGGACCCAAAG	425	usugagUfufhGfufgUfucucuca	317	UUUUUUUUUUUUUUUUUUUU
SRS-000763	457	210	usCfsgagUfufgagUfufhGfagucucsc	102	UACUGGAGAUUGCAGGACCCAAAG	426	csugagUfufhGfufgUfucucuca	318	UUUUUUUUUUUUUUUUUUUU
SRS-000764	460	211	usAfsicagUfufgagUfufhGfagucucsc	103	UAGGAGAUUGCAGGACCCAAAG	427	usugagUfufhGfufgUfucucuca	319	UUUUUUUUUUUUUUUUUUUU
SRS-000765	493	212	usUfsgagUfufgagUfufhGfagucucsc	104	UUUUUUUUUUUUUUUUUUUU	428	csugagUfufhGfufgUfucucuca	320	UUUUUUUUUUUUUUUUUUUU

Duplex ID	Target Position	SEQ ID NO.	Guide/Antisense Structure Code (5'-3')	SEQ ID NO.	Guide/Antisense Base Sequence (5'-3')	SEQ ID NO.	Passenger/Sense Structure Code (5'-3')	SEQ ID NO.	Passenger/Sense Base Sequence (5'-3')
SRS-000766	494	213	usUfsmuuUffggagGfCfcAfgcaugscsc	105	UUUAUUGGGAGGCCACGAUGC	429	csaauuguCfGcFcfUfccaaaataaa	321	CAUCUGGCCTCCCAAUAAAA
SRS-000767	496	214	usGfsccmuuAfhuuggGaGfGgGfGcgacuasg	106	UGCUUUAUUGGAGGCCACAUG	430	ugsucuggCfGcUfcFcftcaaagaacca	322	UGCUGGCCTCCCAAUAAAGA
SRS-000768	498	215	uscHsaegcuUfuuaunGfGfGrAcGfcccagascsa	107	UCA GCUUUAUUGGGAGGCCAGCA	431	cusagggcUfcCcFa fhaaagcuga	323	CUGGCCTCCCAAUAAA GCUGA
SRS-000769	499	216	uscHsaeggUfuuaunUfGfGfAgfagccaugsc	108	UCCAGCUUUAUUGGGAGGCCAGC	432	usggagccuCfCfaAfhuaagcuga	324	UGCGCCTCCCAAUAA AGCUGGA

Note: The target position is relative to human transcript NM_00040.3; the corresponding sequence of a certain SEQ ID NO. is located on its right column of the same row. "A" refers to adenine-3' phosphate; "a" refers to 2'-O-methyladenosine-3' phosphate; "AdP" refers to 2'-deoxyadenosine-3' phosphate; "dA" refers to 2'-fluoroadenosine-3' phosphate; "G" refers to guanosine-3' phosphate; "G" refers to 2'-deoxycytidine-3' phosphate; "dC" refers to 2'-fluorocytidine-3' phosphate; "dC" refers to 2'-deoxyguanosine-3' phosphate; "GU" refers to uridine-3' phosphate; "u" refers to 2'-O-methyluridine-3' phosphate; "UrP" refers to 2'-fluouridine-3' phosphate; "UR" refers to 5-methyluridine-3' phosphate; "m" refers to 2'-O-methyl-deoxyguanosine-3' phosphate; "UTrP" refers to 2'-fluoro-5-methyluridine-3' phosphate; "qT" refers to 2'-deoxythymidine-3' phosphate; "Ts" refers to 3'-phosphothioate. 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.

Table 2. *In vitro* Efficacy of candidate siRNAs

SRS ID	Guide Sequence	Passenger Sequence	Transcript Start Site in NM_000040.3	10 μ M screen MV [% residual target mRNA]	10 μ M screen SD	0.5 μ M screen MV2 [% residual target mRNA]	0.5 μ M screen SD2
SRS-000662	usCfsauggCfaccnCfuGfuUfcccgggsag	cscsaggaAfcAfgAfggugccauga	31	99	13	82	18
SRS-000663	usUfsacccGfgggcUfgCfaUfjggcacscu	gsusgccauUfgCfaGfccccggguua	43	92	5	86	4
SRS-000664	usGfsuaccCfjgggCfuGfcAfuiggcacsc	usgsccanGfcAfgCfcccggguaca	44	97	10	84	3
SRS-000665	usAfsguacCfjgggGfcUfgCfauggcasc	gscscangCfaGfcCfcccggguacua	45	56	19	71	3
SRS-000666	usAfsaggaGfuaccCfjGfgGfucgcasug	usgscagcCfcCfjGfguacuccua	49	91	6	92	7
SRS-000667	usAfscaagGfaguaCfcCfjGfggcuagcsa	csagcccCfjGfgUfacuccungua	51	55	10	64	2
SRS-000668	usAfsacaaGfaguAfcCfcGfjggcuagcsc	asgsccecCfjGfuAfcuccuuuua	52	76	3	83	6

SRS ID	Guide Sequence	Passenger Sequence	Transcript Start Site in NM ₀₀₀₀₄₀ .3	10 μ M screen MV [% residual target mRNA]	10 μ M screen SD	0.5 μ M screen MV2 [% residual target mRNA]	0.5 μ M screen SD2
SRS-000669	usAfsaacAfaaggaGfuAfcCfcggggscsu	cscscggGfuAfcUfccuugugua	54	45	3	63	2
SRS-000670	usAfsacaaCfaaggAfgUfaCfcggggsc	cscscgggUfaCfuCfcuugugua	55	37	3	58	2
SRS-000671	usGfsaacAfaaaGfgAfgUfacccggsg	csgsgguaCfuCfcUfugugugca	57	15	1	28	1
SRS-000672	usGfsgcaaCfaacaAfgGfaGfuacccsgsg	gsgsguacUfcCfuUfguugugcca	58	42	1	63	3
SRS-000673	usGfsggcaAfaaacAfaGfgAfguaccsg	gsgsuacuCfcUfuGfugugugccca	59	47	1	64	6
SRS-000674	usAfsgggcAfaaaCfaAfgGfaGfuacccsc	gusacucCfuUfgUfugugugccua	60	12	0	23	1
SRS-000675	usCfsaggaGfggcaAfcAfaCfaaggasu	uscscungUfuGfuUfgccuccuga	64	37	2	55	2
SRS-000676	usGfsccagGfaggGfaAfcAfaaagsa	csusguuGfuUfgCfcuccuggca	66	50	7	72	2
SRS-000677	usAfsgcucGfggcaGfaGfgCfcaggsgsc	uscscuggCfcUfcUfgcccgagcua	88	80	25	101	7
SRS-000678	usGfsaagcUfgggGfaGfaGfgcagsgsa	csusggccUfcUfgCfcgagcuuca	90	87	8	98	5
SRS-000679	usCfsugaaGfcucGfgGfaGfaggccsag	gsgscucUfgCfcCfagcuucaga	92	88	4	99	7
SRS-000680	usUfscugaAfgcucGfgGfaAfgaggscsa	gscscucGfcCfcGfagcuucagaa	93	101	2	95	5
SRS-000681	usCfscucuGfaagcUfcGfgGfagcagsgsc	csuscucCfcGfaGfauucagagg	95	100	15	101	8
SRS-000682	usGfsgccuChugaaGfcUfcGfaggagsag	csusgccGfaGfcUfucagaggcca	97	76	18	94	4
SRS-000683	usCfsggccUfcugaAfgCfuCfaggcasgsa	usgsgccGfaGfcUfucagaggccga	98	86	11	90	3
SRS-000684	usUfscggcCfucugAfaGfcUfcgggcsag	gscscgaGfcUfuCfagaggccgaa	99	95	9	95	2
SRS-000685	usCfsucggCfcucuGfaAfgCfucgggscsa	cscscgagCfuUfcAfgaggccgaga	100	90	14	87	3
SRS-000686	usAfsuccuGfggcccUfcUfgAfgcucsgsg	gssasgcuCfaGfaGfgccgaggaua	103	93	8	91	5
SRS-000687	usAfsagggAfggcaUfcCfuCfaggccscsu	asgsgccAfgGfaUfgccuccua	112	87	4	97	3
SRS-000688	usGfsaaggGfaggcAfuCfcUfcggccsuc	gsgsgccgaGfgAfuGfucuccuua	113	78	6	100	15
SRS-000689	usAfsaagGfaggGfaUfcCfucggscsu	gscscgagGfaUfgCfcuccuua	114	9	0	22	7
SRS-000690	usGfsagaaGfggagGfcAfuCfcucggscsc	cscsgaggAfuGfcCfucuccuua	115	16	1	30	2
SRS-000691	usCfsuuggUfgcgUfgCfuUfcaugusasa	ascsaugaAfgCfaCfagcccaaga	151	94	4	98	6
SRS-000692	usGfsgucuUfggugGfcGfuCfucucasug	usgsaagcAfcGfcCfaccagaacca	154	93	5	92	4
SRS-000693	usGfscgguCfuuggUfgGfcGfugcuusca	asasgacGfcCfaCfcaagaccgca	156	93	7	92	3

SRS ID	Guide Sequence	Passenger Sequence	Transcript Start Site in NM_000040 .3	10 μ M screen MV [% residual target mRNA]	10 μ M screen SD	0.5 μ M screen MV2 [% residual target mRNA]	0.5 μ M screen SD2
SRS-000694	usGfsgcggUfcuugGfuGfgCfugucususc	asgscacgCfcAfcCfaagaccgccca	157	85	15	96	12
SRS-000695	usUfscuuGfpcggUfcUfuGfguggcsgsu	gscscaccAfaGfaCfcGccaaggaa	162	81	6	99	3
SRS-000696	usCfsauccUfuggcGfgUfcUfugugsgsc	csasccaaGfaCfcGfccaaaggaua	164	72	6	93	3
SRS-000697	usUfsgcauCfcuugGfcGfgUfcuugsgsg	cscsaagaCfcGfcCfaaggaugcaa	166	80	13	105	7
SRS-000698	usGfsugcaUfcuuGfgCfGfucuuugsgsu	csasagacCfcGfcAfaaggaugcaca	167	73	7	84	10
SRS-000699	usCfsgcugCfucagUfgCfaUfcuugsgsc	csasaggaUfgCfaCfugagcagcga	176	72	13	89	6
SRS-000700	usAfsagcuGfcaGfuGfcAfuccuugsg	asasaggaUfcAfcUfgagcagcgua	177	77	4	84	10
SRS-000701	usCfsacgcUfgcucAfgUfgCfauccusug	asgsgaugCfaCfuGfagcagcguga	178	66	12	83	2
SRS-000702	usUfsgcacGfcugcUfcAfgUfgcaucscsu	gfasugcaCfuGfaGfcagcgugcaa	180	69	4	86	5
SRS-000703	usUfsgggaCfuccuGfcAfcGfcugcusc	asgscagcGfuGfcAfggagucccaa	189	65	5	75	5
SRS-000704	usUfscgguCfaccCfGfcCfcugggscsu	gscscaggGfgCfuGfgugaccgaa	222	83	5	92	7
SRS-000705	usAfsucggUfcaccCfaGfcCfcugggscsc	cscsaggGfgCfuGfgugaccgaa	223	70	1	83	8
SRS-000706	usAfsaccaUfcgguCfaCfcCfagccscsu	gsgsgcugGfgUfgAfcCfagggcuca	227	74	2	85	4
SRS-000707	usGfsaagcCfaucGfuCfaCfccagcscsc	gscsugggUfgAfcCfagggcuca	229	70	2	95	8
SRS-000708	usCfsugaaGfccauCfGfuCfaccagsgsc	usgsggugAfcCfGfufugcucacga	231	61	4	83	3
SRS-000709	usAfsaugaAfgccaUfcGfgUfcacccsag	gsgsgugaCfcGfaUfggcuucacga	232	79	18	86	5
SRS-000710	usAfsacugAfgccAfuCfGfufuacccsa	gsgsugacCfGfufuGfucucaguna	233	77	18	90	4
SRS-000711	usGfsaacuGfaagcCfaUfcGfgucacscsc	gssugaccGfaUfgGfucucaguna	234	56	30	79	5
SRS-000712	usGfsgaacUfgaagCfcAfuCfsguacscsc	usggsaccAfuGfgCfucaguuucca	235	53	15	59	3
SRS-000713	usUfscagGfgaacUfgAfaGfcaucsgsg	gssauggcUfuCfaGfucuccugaaa	240	27	19	34	2
SRS-000714	usAfsguagUfcuuCfaGfgCfaacugsasa	csasguncCfcUfgAfaagacuacua	248	64	6	76	4
SRS-000715	usCfsggugCfucaGfuAfgUfcuuncsag	gssaaagaCfuAfcUfggagcacccga	257	83	5	92	3
SRS-000716	usAfsacggUfgcucCfaGfuAfgucunusc	asasgacuAfcUfgGfagcaccguma	259	81	5	83	3
SRS-000717	usUfsaacgGfugcuCfcAfgUfagucususu	asgsacuaCfuGfgAfgcaccgumaa	260	54	7	68	4
SRS-000718	usUfsuaacGfugcUfcCfaGfuagucususu	gssacuacUfgGfaGfaccggunaaa	261	83	17	91	2

[illegible]

SRS ID	Guide Sequence	Passenger Sequence	Transcript Start Site in NM_000040 .3	10 μ M screen MV [% residual target mRNA]	10 μ M screen SD	0.5 μ M screen MV2 [% residual target mRNA]	0.5 μ M screen SD2
SRS-000744	usGfsagauUfgcagGfaCfcCfaaggasgsc	uscscuugGfgUfcCfugcauucua	391	78	3	90	9
SRS-000745	usGfsgagaUfugcaGfgAfcCfcaaggsasg	cscsuugGfgUfcCfugcauucua	392	79	3	81	3
SRS-000746	usUfsggagAftugcAfgGfaCfcaaggsa	csusuggUfcCfugcauucua	393	92	11	95	6
SRS-000747	usCfsuggaGfaugCfaGfgAfcceasgsg	ususggguCfcUfgCfaauuccaga	394	98	12	100	6
SRS-000748	usCfscugAfgauGfcAfgGfaccasasg	usgsugucCfuGfcAfaucuccagga	395	88	4	91	7
SRS-000749	usCfscugGfagauUfgCfaGfgaccsasa	gsgsguccUfgCfaAfuuccagggga	396	91	5	94	3
SRS-000750	usGfscuuGfaggaUfuGfcAfgaccsasa	gsgsuuccGfcAfaUfuccagggga	397	91	3	95	14
SRS-000751	usCfscuuUfuaagCfaAfcCfuacagsgsg	csusguagGfgUfgCfuaaaaggga	422	65	4	86	6
SRS-000752	usGfsuccUfuuaAfgCfaAfcfuacsasg	gssusagguUfgCfuUfaaaaggga	424	77	3	86	3
SRS-000753	usGfsaauCfugucCfcUfuUfuaagcsasa	gscsuuaaAfaGfgGfacagauuca	431	9	1	19	4
SRS-000754	usGfsagaaUfacugUfcCfcUfuuaasgsc	ususaaaGfgGfaCfaguauucua	433	52	2	75	2
SRS-000755	usUfsgagaAfuacuGfuCfcCfuuuasasg	usasaagGfgAfcAfguauucua	434	9	0	20	1
SRS-000756	usCfsugagAfaucUfgUfcCfcuuusasa	asasaagGfaCfaGfuauucucaga	435	9	1	16	2
SRS-000757	usAfsaugaGfaauCfuGfuCfcuuusasa	asasaagGfaCfaGfuauucucaga	436	46	6	65	3
SRS-000758	usCfsacugAfgauAfcUfgUfcuuususu	asasaagGfaCfaGfuAfuucucaguga	437	20	11	27	3
SRS-000759	usGfscacuGfagaaUfaCfuGfuuccususu	asgsaggacAfgUfaUfucucagugca	438	54	10	77	2
SRS-000760	usAfsagacAfcugaGfaAfuAfcugucscsc	gsascaguAfuUfcUfcagugucua	441	24	9	37	1
SRS-000761	usGfsagagCfacugAfgAfaUfacugucscsc	ascsaguaUfuCfuCfagugucua	442	71	8	83	6
SRS-000762	usGfsuaggAfgagcAfcUfgAfgaauascsu	usasuuuUfaGfuGfucuccuaca	446	35	7	32	6
SRS-000763	usCfsaugaGfugggGfgUfaGfgagagcsca	csusuccUfaCfcCfcaccuanga	457	108	10	81	21
SRS-000764	usAfsaggcaUfgaggUfgGfgGfuaggasgsa	uscscuacCfcCfaCfcuacugcua	460	95	6	83	4
SRS-000765	usUfsuauuGfaggGfcCfaGfcaugcsu	gscsaugcUfgGfcCfuuccaauaaa	493	43	17	55	2
SRS-000766	usUfsuauUfgggaGfgCfcAfgcaugscsc	csasugcuGfgCfcUfcccuaaaaa	494	93	9	82	5
SRS-000767	usGfscuuuAfuaggGfaGfgCfcagcasusg	usgscuggCfcUfcCfcauaaaagca	496	116	21	93	5
SRS-000768	usCfsagcuUfuauuGfgGfaGfgccagcsca	csusggccUfcCfcAfauaaagcuga	498	95	22	115	43

SRS ID	Guide Sequence	Passenger Sequence	Transcript Start Site in NM (000040 .3	10 µM screen MV [% residual target mRNA]	10 µM screen SD	0.5 µM screen MV2 [% residual target mRNA]	0.5 µM screen SD2
SRS-000769	usCfscagcUfuauUfgGfgAfgccagsc	usgsgccuCfcCfaAfuuaagcugga	499	71	9	71	6
Note: "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Ap" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cf" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gf" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-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; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate.							

Table 3. Sequence Information for siRNAs Evaluated for their Drug Response Curves

Duplex ID	Target Position	SEQ ID NO.	Guide/Antisense Structure Code (5'-3')	SEQ ID NO.	Guide/Antisense Base Sequence (5'-3')	SEQ ID NO.	Passenger/Sense Structure Code (5'-3')	SEQ ID NO.	Passenger/Sense Base Sequence (5'-3')
SRS-000665	45	457	usAfsuacCfsgggGfUfgCfuaagcsac	433	UAGUACCCGGGGCUGCAUGGCAC	505	gscsaugCfaGfcCfeggguaucua	481	GCCAUGCAGCCCCGGGUACUA
SRS-000667	51	458	usAfsuagGfhuuaCfcCfGfsggugssa	434	UACAAAGGAGUACCCGGGGCUGCA	506	csagcccCfGfGfUfhuucungua	482	CAGCCCCGGGUACUCCUUGUA
SRS-000712	235	459	usGfsgaacUfgagCfcAfcCfsguacsac	435	UGGAACUGAAGGCAUCGUGUACCC	507	usgsaccGfhuGfGfCfhuacguuca	483	UGACCGAUGGGCUUUCAGUUCUA
SRS-000713	240	460	usUfsuagGfhuuaCfcCfGfhuacsac	436	UUUACGGGAACUGAAGCAUCGG	508	gsuugggUfhuCfaGfhuacguuca	484	GAUGGCUUCAGUUCUCCUGAAA
SRS-000717	260	461	usUfsuagCfhuuaCfcCfAfgUfhuacsac	437	UUUACGGGUCUCCAGUAGUCUUU	509	asgsaacCfhuGfGfAfgaccguuaa	485	AGACUACUGGAGGACCGGUAAA
SRS-000723	266	462	usUfsuagCfhuuaCfcCfGfhuacsac	438	UUUCCUUUACGGUGUCUCCAGUA	510	csuugggCfhuCfcGfhuacguuca	486	CUGGAGCAGCGGUUUAAGGACAA
SRS-000753	431	463	usGfsaanaCfhuuaCfcCfUfhuacsac	439	UGAAUACUGUCCCUUUUUAAGCAA	511	gscsuuaaAfaGfGfGfhuacguuca	487	GCUUAAAAGGGACAGAUUUA
SRS-000754	433	464	usGfsaanaCfhuuaCfcCfUfhuacsac	440	UGAAUACUGUCCCUUUUUAAGCAA	512	usuuuaaaCfhuGfGfAfgaccguuca	488	UUAAAAGGGACAGAUUUA
SRS-000755	434	465	usUfsuagGfhuuaCfcCfGfhuacsac	441	UUUAGAAUACUGUCCCUUUUUAAG	513	usuuuaaaCfhuGfGfAfgaccguuca	489	UAAAAGGGACAGAUUUA
SRS-000756	435	466	usCfsuagGfhuuaCfcCfGfhuacsac	442	UCUGAAGAAUACUGUCCCUUUUUA	514	asuuuaaaCfhuGfGfAfgaccguuca	490	AAAAGGGACAGAUUUA

[illegible]

Table 4. Summary of Drug Response Curves for Selected *APOC3* siRNAs

SRS ID	Guide Sequence	Passenger Sequence	IC ₅₀ @ [μM]	IC ₈₀ @ [μM]	MV max KD	SD max KD
SRS-000665	usAfsguacCfcgggGfcUfgCfaungcsasc	gscscangCfaGfcCfcggguacua	0.250	#N/A	63.1	2.7
SRS-000770	usAfs gudAc dCcggggcUfgCfaungcsasc	gscscangCfaGfcCfcggguacua	#N/A	#N/A	50.8	1.1
SRS-000667	usAfscaapGfaenacCfcCfpgGfornpscsa	csascccCfpgGfUfaccuacmuenia	0.175	#N/A	67.3	3.6

SRS ID	Guide Sequence	Passenger Sequence	IC ₅₀ @ [μM]	IC ₈₀ @ [μM]	MV max KD	SD max KD
SRS-000771	usAfscaadAgdGaguaccCfGgGfggcugscsa	csasgccCfGgGfgUfacuccuagua	0.757	#N/A	57.2	1.1
SRS-000712	usGfsgaacUfgaagCfcAfuCfggucascsc	usgsaccgAfuGfGcFuucaguucca	0.050	#N/A	75.1	2.5
SRS-000772	usGfsgadAcdTgaagccAfuCfggucascsc	usgsaccgAfuGfGcFuucaguucca	0.032	#N/A	70.0	4.5
SRS-000713	usUfscugGfgaacUfgAfaGfccaucsgsg	gsasuggcUfuCfaGfuucccugaaa	0.008	0.328	90.1	0.8
SRS-000773	usUfscudAgdGgaacugAfaGfccaucsgsg	gsasuggcUfuCfaGfuucccugaaa	0.003	0.262	88.6	1.2
SRS-000717	usUfsaacGfugcuCfcAfgUfagucususu	asgsacuaCfuGfGafgcaccgunuaa	3.301	#N/A	50.3	3.3
SRS-000774	usUfsaadCgdGuguccAfgUfagucususu	asgsacuaCfuGfGafgcaccgunuaa	0.004	0.633	82.2	3.6
SRS-000723	usUfsgucUfuaacGfgUfgCfuccagsusa	csusggagCfaCfcGfuuaaggacaa	0.008	#N/A	74.0	1.5
SRS-000775	usUfsgudCcdTuaacggUfgCfuccagsusa	csusggagCfaCfcGfuuaaggacaa	0.003	7.839	81.5	1.3
SRS-000753	usGfsaauaCfugucCfcUfuUfuaagcsasa	gscsuuaaAfaGfGfGfacaguanuca	0.002	0.052	96.4	0.4
SRS-000776	usGfisaadTadCuguccUfuUfuaagcsasa	gscsuuaaAfaGfGfGfacaguanuca	0.002	0.048	96.4	0.3
SRS-000754	usGfsgaagUfacugUfcCfcUfuuuaagsgc	ususaaaaGfgGfGfCfaguanuucua	1.077	#N/A	57.3	5.0
SRS-000777	usGfsgagdAadTacugucCfcUfuuuaagsgc	ususaaaaGfgGfGfCfaguanuucua	0.017	2.016	86.1	1.7
SRS-000755	usUfsgagaAfuacuGfuCfcCfuuuuasag	usasaaagGfgAfcAfguaauucuaa	0.001	0.058	93.5	0.5
SRS-000778	usUfsgadGadAuaucugCfcCfuuuuasag	usasaaagGfgAfcAfguaauucuaa	0.000	0.016	95.6	0.2
SRS-000756	usCfsgugAfaaacUfgUfcCfcuuuuasasa	asasaaaggGfaCfaGfuauucucaga	0.000	0.018	95.5	0.4
SRS-000779	usCfsgugdAgaAuaucugUfcCfcuuuuasasa	asasaaaggGfaCfaGfuauucucaga	0.000	0.009	95.8	0.3
SRS-000757	usAfsaugaGfaauaCfuGfuCfccuuususa	asasaggAfcAfgUfaauucucagua	0.062	68.377	73.4	3.6
SRS-000780	usAfsudGadGauacuGfuCfccuuususa	asasaggAfcAfgUfaauucucagua	1.154	#N/A	63.1	4.4
SRS-000758	usCfscugAfgaauAfcUfgUfccuuususu	asasgggaCfaGfuAfuucucaguga	0.004	0.169	89.0	0.6
SRS-000781	usCfscadTgdAgaauacUfgUfccuuususu	asasgggaCfaGfuAfuucucaguga	0.002	0.053	94.5	1.3
Note: the IC50 values for SRS-000755, SRS-000778, SRS-000756, and SRS-000779 were so low (i.e., highly potent) that they were extrapolated by Xlfit, as they are <0.001 μM (lowest dose of assay) "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "g" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "C" refers to uridine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "dG" refers to 2'-deoxycytidine-3'-phosphate; "C" refers to cytosine-3'-phosphate; "c" refers to 2'-O-methylcytosine-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 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "T" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate.						

Note: the IC50 values for SRS-000755, SRS-000778, and SRS-000779 were so low (*i.e.*, highly potent) that they were extrapolated by Xlfit, as they are <0,001 μM (lowest dose of assay). "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Ap" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3-phosphate; "C" refers to cytidine-3'-phosphate; "c" refers to 2'-O-methylcytidine-3'-phosphate; "Cp" refers to 2'-fluorocytidine-3'-phosphate; "dC" refers to 2'-deoxycytidine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gp" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Up" refers to 2'-fluorouridine-3'-phosphate; "I" refers to 5-methyluridine-3'-phosphate; "q" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate.

Table 6. Percentage of Total Cholesterol Relative to Day -4 Following Treatment in Transgenic Mice

Percent Total Cholesterol Relative to Pre-Dose (Day -4)												
SRS ID (Dose)	Statistic	Study Day										
		-4	1	7	14	21	28	35				
PBS	Mean	100.0	101.9	97.7	88.9	94.3	95.9	101.9				
	SD	0.0	19.0	14.6	15.6	11.8	13.1	17.0				
	N	5	5	5	5	5	5	5				
SRS-000231 (0.3mg/kg)	Mean	100.0	159.5	58.6	52.3	60.6	74.2	104.5				
	SD	0.0	55.4	19.4	15.9	19.5	20.6	37.1				
	N	5	5	5	5	5	5	5				
SRS-000231 (1mg/kg)	Mean	100.0	95.8	46.4	43.3	44.4	48.6	48.6				
	SD	0.0	13.7	16.5	16.0	15.1	20.8	9.2				
	N	5	5	5	5	5	5	4				
SRS-000231 (3mg/kg)	Mean	100.0	101.7	47.2	44.7	49.4	49.6	57.1				
	SD	0.0	11.9	14.1	13.2	16.2	15.7	17.3				
	N	5	5	5	5	5	5	5				
SRS-000231 (10mg/kg)	Mean	100.0	131.1	50.2	54.7	53.2	61.6	63.6				
	SD	0.0	81.0	6.8	13.9	7.4	19.0	15.0				
	N	4	4	4	4	4	4	4				
SRS-000228 (0.3mg/kg)	Mean	100.0	107.1	52.7	40.8	42.7	48.2	56.2				
	SD	0.0	22.8	9.6	13.3	10.4	15.6	21.2				
	N	5	5	5	5	5	5	5				
SRS-000228 (1mg/kg)	Mean	100.0	129.9	38.9	36.5	38.5	41.7	43.2				
	SD	0.0	28.8	10.2	14.8	13.0	11.0	19.4				
	N	5	5	5	5	5	5	5				
SRS-000228 (3mg/kg)	Mean	100.0	85.4	37.5	31.0	36.1	33.9	38.1				
	SD	0.0	17.8	28.5	17.8	18.5	17.6	23.5				
	N	5	5	5	5	5	5	5				
SRS-000228 (10mg/kg)	Mean	100.0	96.2	29.4	25.7	26.7	28.3	29.7				

SRS-000229 (1mg/kg)	SD	0.0	19.3	7.3	6.2	6.3	6.3	7.1
	N	5	5	5	5	5	5	5
	Mean	100.0	106.8	38.9	42.6	50.4	60.7	73.8
	SD	0.0	18.2	13.3	17.1	19.3	22.1	20.8
SRS-000229 (3mg/kg)	N	5	5	5	5	5	5	5
	Mean	100.0	124.6	37.6	37.5	40.3	45.8	58.0
	SD	0.0	32.4	10.1	11.0	9.2	10.9	14.3
	N	5	5	5	5	5	5	5
SRS-000229 (10mg/kg)	Mean	100.0	144.6	57.4	47.8	54.5	58.3	68.7
	SD	0.0	80.2	36.7	36.2	35.4	38.8	48.2
	N	5	5	5	4	5	5	5

Table 7. Percentage of Triglycerides Relative to Day -4 Following Treatment in Transgenic Mice

Percent Triglycerides Relative to Pre-Dose (Day -4)											
SRS ID (Dose)	Statistic	Study Day									
		-4	1	7	14	21	28	35			
PBS	Mean	100.0	122.6	478.9	314.9	491.9	116.0	232.0			
	SD	0.0	47.8	249.5	33.0	306.0	19.2	182.8			
	N	5	5	5	5	5	5	5			
SRS-000231 (0.3mg/kg)	Mean	100.0	91.3	68.8	63.6	76.0	120.7	111.1			
	SD	0.0	35.9	33.5	29.0	24.9	24.4	77.0			
	N	5	5	5	5	5	5	5			
SRS-000231 (1mg/kg)	Mean	100.0	157.0	35.8	33.3	34.6	49.7	70.4			
	SD	0.0	95.6	17.0	18.7	15.7	20.5	29.3			
	N	5	5	5	5	5	5	4			
SRS-000231 (3mg/kg)	Mean	100.0	159.1	27.5	29.5	27.5	29.3	41.3			
	SD	0.0	104.3	8.3	11.5	12.4	15.0	18.9			
	N	5	5	5	5	5	5	5			

SRS-000231 (10mg/kg)	Mean	100.0	110.3	22.7	21.7	22.9	27.4	27.4
	SD	0.0	22.3	9.2	7.1	8.2	8.8	4.5
	N	4	4	4	4	4	4	4
SRS-000228 (0.3mg/kg)	Mean	100.0	95.8	168.4	86.1	76.7	95.0	79.6
	SD	0.0	23.1	121.4	12.9	27.5	59.8	21.8
	N	5	5	5	5	5	5	5
SRS-000228 (1mg/kg)	Mean	100.0	163.1	37.4	32.2	44.6	55.2	48.3
	SD	0.0	87.5	7.3	4.4	11.4	10.9	10.7
	N	5	5	5	5	5	5	5
SRS-000228 (3mg/kg)	Mean	100.0	112.1	34.1	27.1	25.4	24.3	29.8
	SD	0.0	25.1	13.1	5.0	7.9	4.7	10.1
	N	5	5	5	5	5	5	5
SRS-000228 (10mg/kg)	Mean	100.0	94.9	27.4	26.1	20.9	31.8	27.3
	SD	0.0	20.2	7.1	6.2	6.9	9.0	9.6
	N	5	5	5	5	5	5	5
SRS-000229 (1mg/kg)	Mean	100.0	112.5	70.9	96.8	100.9	150.7	209.8
	SD	0.0	15.7	17.4	12.0	9.0	75.4	134.6
	N	5	5	5	5	5	5	5
SRS-000229 (3mg/kg)	Mean	100.0	94.8	31.1	32.4	43.2	76.0	71.2
	SD	0.0	17.8	19.1	10.8	27.2	56.5	25.9
	N	5	5	5	5	5	5	5
SRS-000229 (10mg/kg)	Mean	100.0	198.4	53.0	46.8	45.7	67.7	78.3
	SD	0.0	112.7	25.7	10.8	14.7	24.4	28.0
	N	5	5	5	4	5	5	5

Table 8. Percentage of HDL-Cholesterol Relative to Day -4 Following Treatment in Transgenic Mice

Percent HDL-Cholesterol Relative to Pre-Dose (Day -4)											
SRS ID (Dose)	Statistic	Study Day									
		-4	1	7	14	21	28	35			
PBS	Mean	100.0	104.1	73.1	90.8	88.7	108.9	108.9			
	SD	0.0	17.9	37.8	33.7	43.5	38.7	30.9			
	N	5	5	5	5	5	5	5			
SRS-000231 (0.3mg/kg)	Mean	100.0	124.2	143.5	158.6	149.2	116.3	159.1			
	SD	0.0	26.9	54.9	64.4	59.4	59.9	49.4			
	N	5	5	5	5	5	5	5			
SRS-000231 (1mg/kg)	Mean	100.0	103.1	173.8	167.1	174.0	164.3	177.3			
	SD	0.0	34.6	57.7	51.9	60.7	48.1	43.3			
	N	5	5	5	5	5	5	4			
SRS-000231 (3mg/kg)	Mean	100.0	90.0	165.0	152.1	167.8	167.2	185.6			
	SD	0.0	18.8	35.8	23.5	24.1	21.1	32.2			
	N	5	5	5	5	5	5	5			
SRS-000231 (10mg/kg)	Mean	100.0	131.8	211.4	220.4	217.8	235.9	250.7			
	SD	0.0	24.7	77.3	103.1	94.7	103.4	107.1			
	N	4	4	4	4	4	4	4			
SRS-000228 (0.3mg/kg)	Mean	100.0	92.4	86.2	102.2	124.2	106.1	99.5			
	SD	0.0	15.3	22.3	10.5	35.9	38.7	35.6			
	N	5	5	5	5	5	5	5			
SRS-000228 (1mg/kg)	Mean	100.0	108.2	196.7	174.7	174.2	176.0	183.3			
	SD	0.0	28.3	28.1	29.9	28.0	16.3	31.3			
	N	5	5	5	5	5	5	5			
SRS-000228 (3mg/kg)	Mean	100.0	83.2	122.2	108.4	128.3	119.7	132.7			
	SD	0.0	18.9	29.0	13.0	16.0	14.4	22.3			
	N	5	5	5	5	5	5	5			
SRS-000228 (10mg/kg)	Mean	100.0	99.9	161.1	140.0	151.6	149.9	169.0			

SRS-000229 (1mg/kg)	SD	0.0	13.4	24.5	24.1	15.0	24.0	25.7
	N	5	5	5	5	5	5	5
	Mean	100.0	94.7	120.2	115.5	127.1	88.1	100.5
	SD	0.0	26.2	44.5	37.1	46.3	31.3	44.7
	N	5	5	5	5	5	5	5
SRS-000229 (3mg/kg)	Mean	100.0	128.7	198.0	180.9	167.9	148.1	144.8
	SD	0.0	36.3	139.6	92.2	70.4	75.3	52.6
	N	5	5	5	5	5	5	5
	Mean	100.0	105.7	172.0	157.7	171.6	161.5	185.2
	SD	0.0	26.6	48.9	55.1	52.3	49.7	62.5
SRS-000229 (10mg/kg)	N	5	5	5	4	5	5	5

Table 9. Percentage of LDL-Cholesterol Relative to Day -4 Following Treatment in Transgenic Mice

SRS ID (Dose)	Statistic	Percent LDL-Cholesterol Relative to Pre-Dose (Day -4)							
		Study Day							
		-4	1	7	14	21	28	35	
PBS	Mean	100.0	115.3	207.3	67.1	259.0	117.6	93.4	
	SD	0.0	94.6	192.0	38.1	236.1	38.7	62.2	
	N	5	5	5	5	5	5	5	
SRS-000231 (0.3mg/kg)	Mean	100.0	60.2	64.8	43.4	62.2	116.2	130.1	
	SD	0.0	72.2	18.8	24.3	25.6	31.5	85.6	
	N	5	5	5	5	5	5	4	
SRS-000231 (1mg/kg)	Mean	100.0	115.7	47.7	19.5	16.9	22.0	37.4	
	SD	0.0	42.0	18.7	6.6	5.2	4.6	6.5	
	N	5	5	5	5	5	5	4	
SRS-000231 (3mg/kg)	Mean	100.0	157.0	64.9	32.4	21.6	20.2	27.6	

SRS-000231 (10mg/kg)	SD	0.0	125.7	18.3	27.6	6.1	6.2	6.6
	N	5	5	5	5	5	5	5
	Mean	100.0	74.9	43.2	14.8	14.4	38.4	14.4
	SD	0.0	20.1	19.7	6.4	6.6	25.8	6.6
	N	4	4	4	4	4	4	4
SRS-000228 (0.3mg/kg)	Mean	100.0	65.8	84.0	37.1	37.0	49.9	55.1
	SD	0.0	35.1	76.8	12.9	33.1	36.8	40.8
	N	5	5	5	5	5	5	5
	Mean	100.0	330.8	70.4	44.0	39.4	60.8	55.1
	SD	0.0	550.5	68.8	49.0	45.5	73.6	72.0
SRS-000228 (3mg/kg)	N	5	5	5	5	5	5	5
	Mean	100.0	72.4	58.2	19.4	19.6	19.4	22.4
	SD	0.0	49.3	36.6	12.2	11.9	12.2	16.2
	N	5	5	5	5	5	5	5
	Mean	100.0	155.6	72.7	24.2	44.2	26.0	29.3
SRS-000228 (10mg/kg)	SD	0.0	100.3	48.9	16.3	59.6	18.9	22.5
	N	5	5	5	5	5	5	5
	Mean	100.0	86.0	41.5	41.6	51.4	128.6	117.0
	SD	0.0	47.4	16.6	16.8	23.4	61.7	42.6
	N	5	5	5	5	5	5	5
SRS-000229 (3mg/kg)	Mean	100.0	79.0	69.0	33.1	49.4	111.0	54.0
	SD	0.0	52.8	70.1	34.1	79.4	192.2	38.4
	N	5	5	5	5	5	5	5
	Mean	100.0	272.3	90.1	30.0	53.2	37.1	48.3
	SD	0.0	179.1	70.8	23.6	47.9	25.1	34.4
SRS-000229 (10mg/kg)	N	5	5	5	5	5	5	5

Table 10. Percentage of Plasma APOC3 Relative to Day 1 Following Treatment in Transgenic Mice

Percent Plasma APOC3 Relative to Day 1									
SRS ID (Dose)	Statistic	Study Day							
		1	7	14	21	28	35		
PBS	Mean	100.0	91.0	75.4	75.6	106.5	96.9		
	SD	3.9	10.1	6.3	5.1	8.6	11.2		
	N	1	5	5	2	5	5		
SRS-000231 (0.3 mg/kg)	Mean	100.0	47.9	42.7	43.7	84.2	91.3		
	SD	10.9	20.7	8.0	7.7	12.8	14.0		
	N	4	5	5	3	4	5		
SRS-000231 (1 mg/kg)	Mean	100.0	23.8	24.9	28.5	48.2	56.6		
	SD	21.7	8.8	6.8	9.2	9.0	10.9		
	N	2	5	5	5	4	4		
SRS-000231 (3 mg/kg)	Mean	100.0	22.1	22.2	21.9	47.5	43.4		
	SD	27.3	3.5	2.8	2.6	7.5	8.1		
	N	3	5	5	5	5	5		
SRS-000231 (10 mg/kg)	Mean	100.0	17.7	22.0	23.2	45.6	34.2		
	SD	7.1	6.5	1.9	1.5	5.4	2.0		
	N	1	4	4	2	3	4		
SRS-000228 (0.3 mg/kg)	Mean	100.0	62.6	41.2	49.1	57.6	65.7		
	SD	10.7	18.7	4.5	16.5	19.1	18.3		
	N	3	5	5	4	5	5		
SRS-000228 (1 mg/kg)	Mean	100.0	24.6	16.9	23.8	39.3	38.6		
	SD	4.8	2.4	2.8	3.8	10.0	4.6		
	N	2	5	4	4	5	5		
SRS-000228 (3 mg/kg)	Mean	100.0	28.0	16.6	16.5	34.1	32.3		
	SD	14.8	3.0	2.2	2.4	8.4	8.2		
	N	3	5	5	1	5	5		
SRS-000228 (10 mg/kg)	Mean	100.0	18.2	11.5	11.7	19.2	22.7		

SRS-000229 (1 mg/kg)	SD	13.0	3.2	1.5	2.8	1.9	3.3
	N	4	5	5	3	5	5
	Mean	100.0	42.6	39.7	43.7	79.5	87.0
	SD	9.0	9.6	5.7	4.7	7.4	11.4
SRS-000229 (3 mg/kg)	N	5	5	5	5	5	5
	Mean	100.0	22.8	26.5	30.0	60.8	74.0
	SD	13.6	9.3	8.2	11.7	18.7	23.2
	N	2	5	5	5	5	5
SRS-000229 (10 mg/kg)	Mean	100.0	19.6	18.6	21.3	35.1	43.5
	SD	12.7	5.1	3.0	1.9	7.2	6.9
	N	4	5	5	2	5	5

Table 11. Percent Remaining APOC3 mRNA Relative to PBS Control Following Treatment in Transgenic Mice

% Remaining APOC3 mRNA on Day 35 Relative to PBS						
SRS ID	Statistic	Dose Level				
		0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	
SRS-000231	Mean	67.7	45.4	8.5	3.3	
	SD	19.5	27.3	1.8	1.6	
	N	5	4	5	4	
SRS-000228	Mean	21.2	16.2	9.7	3.8	
	SD	4.5	5.0	4.5	1.8	
	N	5	5	5	5	
SRS-000229	Mean	-	22.7	19.1	10.5	
	SD	-	6.4	5.6	2.9	
	N	-	5	5	5	

Table 12. Additional siRNA sequences evaluated in Example 5

Duplex ID	SEQ ID NO	Guide/antisense Structure Code (5'-3')	SEQ ID NO	Guide/antisense Base Sequence (5'-3')	SEQ ID NO	Passenger/sense Structure Code (5'-3')	SEQ ID NO	Passenger/sense Base Sequence (5'-3')
SRS-000231	564	usCfsugagAfaaacUfgUfcCfeunusasa	553	UCUGAGAAUACUGUCCCUUUUAA	586	asasaaggGfaCfaGfhamucueaga	575	AAAAAGGACAGAUUUUCUCAGA
SRS-001860	565	ypusCfsugagAfaaacUfgUfcCfeunusasa	554	UCUGAGAAUACUGUCCCUUUUAA	587	asasaaggGfaCfaGfhamucueaga	576	AAAAAGGACAGAUUUUCUCAGA
SRS-001861	566	usCfsugagAfaaacUfgUfcCfeunusasa	555	UCUGAGAAUACUGUCCCUUUUAA	588	gsasaaggGfaCfaGfhamucueaga	577	GAAAAGGACAGAUUUUCUCAGA
SRS-001862	567	usCfsugagAfaaacUfgUfcCfeunusasa	556	UCUGAGAAUACUGUCCCUUUUAA	589	csasaaggGfaCfaGfhamucueaga	578	CAAAAGGACAGAUUUUCUCAGA
SRS-001863	568	usCfsugagAfaaacUfgUfcCfeunusasa	557	UCUGAGAAUACUGUCCCUUUUAA	590	gsasaaggGfaCfaGfhamucueaga	579	GCAAAGGACAGAUUUUCUCAGA
SRS-001864	569	usCfsugagAfaaacUfgUfcCfeunusasa	558	UCUGAGAAUACUGUCCCUUUUAA	591	csasaaggGfaCfaGfhamucueaga	580	CGAAAGGACAGAUUUUCUCAGA
SRS-001865	570	usCfsugagAfaaacUfgUfcCfeunusasa	559	UCUGAGAAUACUGUCCCUUUUAA	592	(invAB)asasaaggGfaCfaGfhamucueaga	581	AAAAAGGACAGAUUUUCUCAGA
SRS-001866	571	usCfsugagAfaaacUfgUfcCfeunusasa	560	UCUGAGAAUACUGUCCCUUUUAA	593	(invAB)csasaaggGfaCfaGfhamucueaga	582	CAAAAGGACAGAUUUUCUCAGA
SRS-001868	572	usCfsugagAfaaacUfgUfcCfeunusasa	561	UCUGAGAAUACUGUCCCUUUUAA	594	asasaaggGfaCfaGfhamucueaga	583	AAAAAGGACAGAUUUUCUCAGA
SRS-001869	573	usCfsugagAfaaacUfgUfcCfeunusasa	562	UCUGAGAAUACUGUCCCUUUUAA	595	asasaaggGfaCfaGfhamucueaga	584	AAAAAGGACAGAUUUUCUCAGA
SRS-001870	574	usCfsugagAfaaacUfgUfcCfeunusasa	563	UCUGAGAAUACUGUCCCUUUUAA	596	asasaaggGfaCfaGfhamucueaga	585	AAAAAGGACAGAUUUUCUCAGA

Note: the target position of each of the sequences listed in Table 12 is 435' (relative to human transcript NM_000040.3); the corresponding sequence of a certain SEQ ID NO. is located on its right column of the same row. "A" refers to adenosine-3'-phosphate; "a" refers to 2'-O-methyladenosine-3'-phosphate; "Ap" refers to 2'-fluoroadenosine-3'-phosphate; "dA" refers to 2'-deoxyadenosine-3'-phosphate; "C" refers to cytosine-3'-phosphate; "c" refers to 2'-O-methylcytosine-3'-phosphate; "Cp" refers to 2'-fluorocytosine-3'-phosphate; "dC" refers to 2'-deoxycytosine-3'-phosphate; "G" refers to guanosine-3'-phosphate; "g" refers to 2'-O-methylguanosine-3'-phosphate; "Gp" refers to 2'-fluoroguanosine-3'-phosphate; "dG" refers to 2'-deoxyguanosine-3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Up" refers to 2'-fluorouridine-3'-phosphate; "dU" refers to 2'-deoxyuridine-3'-phosphate; "P" refers to 5'-phosphate; "p" refers to 2'-O-methyl-5'-phosphate; "Pp" refers to 2'-fluoro-5'-phosphate; "dP" refers to 2'-deoxy-5'-phosphate; "S" refers to 3'-phosphorothioate, "(invAB)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide. Each modified sense sequence is coupled to a targeting moiety (e.g., GalNAc) at its 3' end via a linker (e.g., Formula V', V'', V''', V''', or V''').

Table 13. Percentage of Total Cholesterol Relative to Day 1 Following Treatment in Transgenic Mice

Percent Total Cholesterol Relative to Day 1											
SRS ID	Statistics	Study Day									
		1	7	14	21	28	35	42	49	56	
1x PBS	Mean	100.0	113.2	109.8	119.0	98.6	104.8	98.5	99.0	99.5	
	SD	0.0	19.6	20.6	32.4	87.8	27.7	24.0	19.9	21.2	
	N	5	5	5	5	5	5	5	5	5	
SRS-000231	Mean	100.0	29.9	40.1	34.9	61.2	31.3	33.2	31.3	30.7	

	SD	0.0	12.9	11.4	15.8	33.1	12.3	12.4	12.6	10.3
	N	4	4	3	4	4	4	4	4	4
SRS-001860	Mean	100.0	46.3	64.1	64.0	55.4	53.2	53.7	43.3	41.5
	SD	0.0	20.3	34.5	36.5	28.0	27.4	24.7	18.0	16.7
	N	4	4	4	4	4	4	4	4	4
	Mean	100.0	49.7	58.0	56.9	57.2	53.6	51.5	47.2	46.7
SRS-001861	SD	0.0	19.5	22.9	21.3	22.8	20.4	19.3	16.4	15.9
	N	5	5	5	5	5	5	5	5	5
	Mean	100.0	56.4	60.9	64.2	61.3	58.1	54.4	51.6	48.9
	SD	0.0	29.7	26.8	32.6	29.9	28.6	26.1	24.4	23.7
SRS-001862	N	5	5	5	5	5	5	5	5	5
	Mean	100.0	49.1	63.2	50.6	50.7	47.1	50.2	49.4	46.6
	SD	0.0	28.4	33.1	25.7	26.8	22.7	27.1	27.8	26.1
	N	5	5	5	5	5	5	5	5	5
SRS-001863	Mean	100.0	39.3	46.3	45.5	47.4	49.3	49.0	50.4	45.9
	SD	0.0	19.1	19.0	18.4	21.8	20.4	21.5	20.8	17.6
	N	5	5	5	5	5	5	5	5	5
	Mean	100.0	50.8	57.9	55.8	57.6	52.7	55.5	49.9	63.2
SRS-001865	SD	0.0	17.8	18.7	20.5	20.5	16.2	18.4	17.0	36.4
	N	5	5	5	5	5	5	5	5	5
	Mean	100.0	43.6	56.6	54.7	58.1	54.2	56.0	52.3	51.9
	SD	0.0	21.3	30.4	27.8	30.1	31.2	31.4	30.1	35.5
SRS-001866	N	5	4	4	4	4	4	4	4	4
	Mean	100.0	37.2	42.8	38.0	37.5	33.0	36.2	33.2	31.2
	SD	0.0	11.8	15.6	11.4	13.8	12.4	12.2	12.4	10.8
	N	5	5	5	5	5	5	5	5	5
SRS-001868	Mean	100.0	47.9	48.9	47.0	47.9	44.0	46.4	42.6	40.3
	SD	0.0	21.4	25.5	22.7	26.2	22.7	24.1	20.7	16.9
	N	4	4	4	4	4	4	4	4	4
	Mean	100.0	36.1	54.1	45.1	44.5	38.2	38.8	38.9	39.2

	SD	0.0	14.5	28.8	12.7	15.0	13.1	11.9	12.8	12.5
	N	4	4	4	4	3	3	3	3	3

Table 14. Percentage of Triglycerides Relative to Day 1 Following Treatment in Transgenic Mice

SRS ID	Statistics	Percent Triglycerides Relative to Day 1									
		Study Day									
		1	7	14	21	28	35	42	49	56	
1x PBS	Mean	100.0	182.5	158.6	361.0	186.5	135.8	202.7	297.7	204.0	
	SD	0.0	137.6	118.1	324.5	188.8	70.5	182.9	197.3	239.1	
	N	5	5	5	5	5	5	5	5	5	
SRS-000231	Mean	100.0	10.0	15.9	12.4	43.6	9.7	14.9	13.2	18.8	
	SD	0.0	4.8	6.8	8.5	42.0	5.2	5.3	6.0	7.0	
	N	4	4	3	4	4	4	4	4	4	
SRS-001860	Mean	100.0	12.0	20.5	12.5	11.9	10.4	16.7	9.7	15.0	
	SD	0.0	5.6	17.4	6.2	5.5	5.3	10.1	6.1	8.0	
	N	4	4	4	4	4	4	4	4	4	
SRS-001861	Mean	100.0	12.9	20.8	21.9	19.8	21.2	22.0	17.6	26.8	
	SD	0.0	8.3	13.8	16.5	12.9	18.2	15.7	12.2	22.4	
	N	5	5	5	5	5	5	5	5	5	
SRS-001862	Mean	100.0	12.2	22.7	25.6	19.0	19.3	24.2	17.0	22.6	
	SD	0.0	4.4	12.4	14.7	8.4	13.1	14.9	7.5	14.2	
	N	5	5	5	5	5	5	5	5	5	
SRS-001863	Mean	100.0	14.2	20.0	25.1	19.7	19.0	24.3	26.5	25.7	
	SD	0.0	17.2	26.1	38.2	22.3	26.6	28.7	37.4	31.0	
	N	5	5	5	5	5	5	5	5	5	
SRS-001864	Mean	100.0	17.7	27.7	18.0	19.9	16.6	25.9	18.7	19.7	
	SD	0.0	8.6	12.3	8.0	6.2	8.2	11.3	9.1	8.8	
	N	5	5	5	5	5	5	5	5	5	

SRS-001865	Mean	100.0	14.8	27.8	16.2	23.3	24.4	24.9	32.6	39.2
	SD	0.0	7.5	13.9	4.7	13.7	9.8	5.2	12.1	12.0
	N	5	5	5	5	5	5	5	5	5
SRS-001866	Mean	100.0	13.3	20.5	21.3	18.8	14.9	20.0	17.7	23.6
	SD	0.0	5.6	8.7	9.6	6.1	5.0	8.6	8.5	18.3
	N	5	4	4	4	4	4	4	4	4
SRS-001868	Mean	100.0	20.5	28.7	22.5	18.9	18.3	25.8	18.9	23.7
	SD	0.0	11.6	15.5	12.0	7.7	8.0	14.9	7.6	10.3
	N	5	5	5	5	5	5	5	5	5
SRS-001869	Mean	100.0	12.7	17.4	20.0	20.8	17.0	29.0	17.3	21.5
	SD	0.0	7.1	11.5	11.0	19.9	15.0	32.3	13.1	11.3
	N	4	4	4	4	4	4	4	4	4
SRS-001870	Mean	100.0	15.6	24.3	19.8	21.6	10.1	20.9	14.8	19.1
	SD	0.0	10.3	16.0	13.9	20.2	8.1	21.1	13.1	15.3
	N	4	4	4	4	3	3	3	3	3

Table 15. Percentage of HDL-Cholesterol Relative to Day 1 Following Treatment in Transgenic Mice

SRS ID	Statistics	Percent HDL-Cholesterol Relative to Day 1									
		Study Day									
		1	7	14	21	28	35	42	49	56	
1x PBS	Mean	100.0	107.6	94.9	104.6	109.2	102.1	91.5	77.5	87.4	
	SD	0.0	23.4	18.0	28.4	42.1	28.1	23.9	22.1	31.8	
	N	5	5	5	5	5	5	5	5	5	
SRS-000231	Mean	100.0	208.2	248.3	244.9	195.2	219.7	223.8	206.4	196.7	
	SD	0.0	107.1	97.8	142.6	143.6	114.7	110.9	98.1	109.8	
	N	4	4	3	4	4	4	4	4	4	
SRS-001860	Mean	100.0	258.7	292.7	277.1	243.2	243.1	260.1	227.0	213.6	
	SD	0.0	190.7	232.7	184.1	163.6	165.3	178.1	150.8	138.5	
	N	4	4	4	4	4	4	4	4	4	

SRS-001861	Mean	100.0	202.6	210.7	215.6	209.0	195.5	200.3	191.0	191.7
	SD	0.0	78.3	85.1	76.7	79.0	67.7	71.3	77.8	72.6
	N	5	5	5	5	5	5	5	5	5
SRS-001862	Mean	100.0	178.7	178.7	185.5	181.8	169.5	168.7	158.6	160.7
	SD	0.0	65.9	72.1	59.7	67.3	60.9	60.6	60.0	55.8
	N	5	5	5	5	5	5	5	5	5
SRS-001863	Mean	100.0	171.9	194.9	176.7	174.3	159.6	174.1	159.1	159.6
	SD	0.0	104.8	136.8	116.7	102.5	96.8	100.8	93.1	89.3
	N	5	5	5	5	5	5	5	5	5
SRS-001864	Mean	100.0	125.8	140.7	149.1	147.7	148.4	153.8	153.6	147.3
	SD	0.0	45.1	41.5	48.1	44.6	44.5	46.2	51.2	47.2
	N	5	5	5	5	5	5	5	5	5
SRS-001865	Mean	100.0	221.6	229.1	244.4	245.3	218.2	228.3	195.7	209.1
	SD	0.0	74.3	79.3	84.8	83.0	68.7	74.9	71.6	106.1
	N	5	5	5	5	5	5	5	5	5
SRS-001866	Mean	100.0	167.5	191.0	197.7	211.6	196.7	201.4	184.3	163.2
	SD	0.0	62.2	69.6	64.1	74.2	65.5	67.4	63.1	59.2
	N	5	4	4	4	4	4	4	4	4
SRS-001868	Mean	100.0	179.9	184.5	184.4	178.4	158.9	180.8	161.4	157.9
	SD	0.0	67.8	84.0	80.5	82.8	73.2	79.2	59.9	69.4
	N	5	5	5	5	5	5	5	5	5
SRS-001869	Mean	100.0	193.3	187.5	193.1	196.6	175.3	183.5	171.8	172.2
	SD	0.0	103.6	79.6	89.2	95.0	80.0	70.2	68.4	77.9
	N	4	4	4	4	4	4	4	4	4
SRS-001870	Mean	100.0	201.3	289.8	223.7	229.3	205.8	202.6	203.1	200.4
	SD	0.0	169.8	305.8	163.1	203.6	186.7	174.1	179.8	179.0
	N	4	4	4	4	3	3	3	3	3

Table 16. Percentage of LDL-Cholesterol Relative to Day 1 Following Treatment in Transgenic Mice

SRS ID	Statistics	Percent LDL-Cholesterol Relative to Day 1									
		Study Day									
		1	7	14	21	28	35	42	49	56	
1x PBS	Mean	100.0	120.7	55.4	59.3	99.4	71.1	63.4	109.7	64.1	
	SD	0.0	56.2	32.5	42.0	126.8	31.6	36.9	127.2	64.0	
	N	5	5	5	5	5	5	5	5	5	
SRS-000231	Mean	100.0	4.8	6.0	5.2	38.4	4.7	4.9	4.8	6.6	
	SD	0.0	1.9	1.2	2.4	49.3	2.0	1.8	1.9	2.4	
	N	4	4	3	4	4	4	4	4	4	
SRS-001860	Mean	100.0	4.6	7.4	9.0	7.7	5.9	6.9	4.2	6.3	
	SD	0.0	1.7	5.1	6.2	4.7	3.6	3.8	1.9	3.3	
	N	4	4	4	4	4	4	4	4	4	
SRS-001861	Mean	100.0	12.6	14.9	15.0	23.3	13.3	12.8	12.2	13.5	
	SD	0.0	12.7	13.9	13.1	14.0	12.7	12.2	12.6	13.0	
	N	5	5	5	5	5	5	5	5	5	
SRS-001862	Mean	100.0	14.3	19.0	21.6	22.3	15.1	15.7	13.5	14.3	
	SD	0.0	14.1	22.5	22.5	18.1	14.6	14.7	13.9	13.7	
	N	5	5	5	5	5	5	5	5	5	
SRS-001863	Mean	100.0	17.0	17.4	22.9	18.8	17.4	17.3	19.7	20.1	
	SD	0.0	18.9	18.5	29.5	21.2	18.5	18.7	24.3	22.0	
	N	5	5	5	5	5	5	5	5	5	
SRS-001864	Mean	100.0	9.0	9.1	9.0	9.0	9.0	9.0	9.0	9.0	
	SD	0.0	5.8	5.7	5.8	5.8	5.8	5.8	5.8	5.8	
	N	5	5	5	5	5	5	5	5	5	
SRS-001865	Mean	100.0	16.0	16.5	16.0	24.0	16.2	16.3	17.1	30.0	

	SD	0.0	10.8	10.8	10.8	15.5	10.6	10.5	9.6	29.6
	N	5	5	5	5	5	5	5	5	5
	Mean	100.0	12.4	12.4	12.4	23.7	22.7	12.4	12.4	13.8
	SD	0.0	7.6	7.6	7.6	26.1	26.6	7.6	7.6	8.3
SRS-001866	N	5	4	4	4	4	4	4	4	4
	Mean	100.0	5.3	6.3	5.4	7.1	5.3	5.6	5.2	5.4
	SD	0.0	4.0	3.5	4.0	5.1	4.0	4.0	4.0	3.9
	N	5	5	5	5	5	5	5	5	5
SRS-001868	Mean	100.0	13.6	13.5	13.9	39.0	13.5	13.5	13.5	13.5
	SD	0.0	18.4	18.5	18.2	56.7	18.5	18.5	18.5	18.5
	N	4	4	4	4	4	4	4	4	4
	Mean	100.0	7.0	9.4	7.5	9.9	6.9	6.9	6.9	7.2
SRS-001870	SD	0.0	5.1	5.2	4.6	7.0	6.2	6.2	6.2	6.0
	N	4	4	4	4	3	3	3	3	3

Table 17. Percentage of Plasma APOC3 Relative to Day 1 Following Treatment in Transgenic Mice

SRS ID	Percent Plasma APOC3 Relative to Day 1										
	Statistics	Study Day									
		1	7	14	21	28	35	49	56		
1x PBS	Mean	100.0	119.8	112.2	97.5	68.6	68.5	65.1	59.5		
	SD	2.8	12.6	16.7	16.1	20.0	15.6	17.9	14.0		
	N	5	4	4	5	5	4	5	5		
SRS-000231	Mean	100.0	26.5	30.4	25.6	11.4	11.0	12.7	19.5		
	SD	3.0	5.2	6.2	10.9	6.9	4.0	6.7	9.8		
	N	5	3	4	3	4	4	4	4		
SRS-001860	Mean	100.0	35.2	29.8	22.6	10.7	7.2	10.7	11.6		
	SD	5.3	2.9	6.0	6.7	1.5	2.3	2.5	1.7		
	N	4	3	4	3	5	5	4	5		
SRS-001861	Mean	100.0	30.2	35.2	23.1	16.5	9.0	13.9	12.5		

SRS-001862	SD	4.4	8.3	5.5	7.5	3.9	2.9	3.4	3.8
	N	5	3	4	3	4	5	5	5
	Mean	100.0	38.8	34.1	29.4	14.9	9.2	11.8	13.0
	SD	5.0	11.6	4.0	4.2	4.2	2.5	2.1	3.5
	N	4	5	4	4	5	5	5	5
SRS-001863	Mean	100.0	27.6	35.5	20.6	10.7	7.9	13.3	10.0
	SD	3.3	8.7	13.8	4.8	5.0	4.5	6.8	5.0
	N	5	5	5	5	5	5	4	5
	Mean	100.0	28.9	37.6	25.7	10.8	7.6	12.8	9.7
	SD	2.7	10.6	8.2	6.8	2.5	2.0	3.2	2.5
SRS-001864	N	5	5	5	5	5	5	5	5
	Mean	100.0	38.3	45.3	34.2	12.7	9.6	27.1	25.0
	SD	4.0	14.1	12.6	8.5	2.6	3.3	8.8	15.4
	N	5	5	5	5	5	5	5	4
	Mean	100.0	25.2	33.3	23.8	13.1	5.2	10.3	11.0
SRS-001866	SD	4.2	5.1	17.9	4.4	3.8	2.5	1.9	5.5
	N	5	4	2	4	4	2	4	5
	Mean	100.0	28.6	40.0	25.9	7.2	5.6	14.4	7.4
	SD	5.7	6.7	3.7	5.3	2.1	1.9	7.2	1.7
	N	5	3	4	2	4	5	5	5
SRS-001868	Mean	100.0	31.6	41.8	25.5	13.9	7.0	15.6	17.8
	SD	2.9	10.4	15.3	12.1	2.9	2.0	2.2	3.2
	N	4	3	3	4	3	3	2	3
	Mean	100.0	19.9	34.6	26.0	9.5	8.3	13.2	14.5
	SD	7.0	3.9	6.2	7.5	1.4	1.7	2.3	3.5
SRS-001870	N	4	3	3	4	4	3	3	3

Table 18. APOC3 mRNA Expression Relative to PBS Control Following Treatment in Transgenic Mice

Relative Expression of Liver APOC3 mRNA		
SRS ID	Statistics	Day 56 Results
1x PBS	Mean	1.01
	SD	0.11
	N	3
SRS-000231	Mean	0.26
	SD	0.16
	N	5
SRS-001860	Mean	0.07
	SD	0.06
	N	4
SRS-001861	Mean	0.05
	SD	0.04
	N	5
SRS-001862	Mean	0.03
	SD	0.01
	N	5
SRS-001863	Mean	0.06
	SD	0.06
	N	5
SRS-001864	Mean	0.13
	SD	0.11
	N	5
SRS-001865	Mean	0.62
	SD	0.35
	N	4
SRS-001866	Mean	0.12

SRS-001868	SD	0.05
	N	4
	Mean	0.14
	SD	0.06
SRS-001869	N	5
	Mean	0.21
	SD	0.10
	N	4
SRS-0018670	Mean	0.18
	SD	0.11
	N	3

CLAIMS**WHAT IS CLAIMED IS:**

1. A polynucleic acid molecule for modulating expression of apolipoprotein C3 (*APOC3*) 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% identical to a nucleic acid sequence selected from SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563.
2. The polynucleic acid molecule of claim 1, 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: 1-108, 433-456, 529-534, and 553-563 with no more than 1, 2, 3, or 4 mismatches.
3. The polynucleic acid molecule of claim 1 or 2, 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: 217-324, 481-504, 541-546, and 575-585.
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 of a nucleic acid sequence selected from SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 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 a nucleic acid sequence of SEQ ID NOs: 217-324, 481-504, 541-546, and 575-585 and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 1-108, 433-456, 529-534, and 553-563.
6. The polynucleic acid molecule of any one of claims 1-5, wherein the polynucleic acid molecule comprises (1) a 2'-fluoro modified nucleotides; (2) a 2'-O-methyl modified nucleotides; (3) 2'-deoxy modified nucleotides, or (4) a modified internucleotide linkage.
7. The polynucleic acid molecule of claim 6, wherein the polynucleic acid molecule comprise at least two consecutive modified internucleotide linkages at the 5' end or at the 3' end.
8. The polynucleic acid molecule of any one of claims 6-7, wherein the antisense strand comprises 5' - nNfnnnNfnNfNfnnnnNfnNfnnnnnnn-3', 5' - nNfnnnNfnnnnnnnNfnNfnnnnnnn-3', 5' - nNfnnnnNfnnnnNfnNfnnnnnnnn-3', 5' - nNfnnnnNfnnnnNfnNfnNfnnnnnnn-3', or 5' -

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

9. The polynucleic acid molecule of any one of claims 6-8, wherein the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', or 5'-nnnnnnnnNfnNfnNfnnnnnnnnn-3', wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.
10. The polynucleic acid molecule of any one of claims 6-9, wherein
 - i) the sense strand comprises 5'-NfnNfnNfnNfnNfnNfnNfnNfnNfnNf-3', the antisense strand comprises 5'-nNfnNfnNfnNfnNfnnnNfnNfnNfnNfnn-3';
 - ii) the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', the antisense strand comprises 5'-nNfnnnNfnNfnNfnnnNfnNfnnnnnnn-3';
 - iii) the sense strand comprises 5'-nnnnnnnnNfnNfnnnnnnnnn-3', wherein the antisense strand comprises 5'-nNfnnnnnnnnnNfnNfnnnnnnnnn-3';
 - iv) the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', the antisense strand comprises 5'-nNfnnnnnnnnnNfnNfnNfnnnnnnn-3'; or
 - v) the sense strand comprises 5'-nnnnnnNfnNfnNfnnnnnnnnn-3', the antisense strand comprises 5'-nNfnnnnnNfnnnNfnNfnNfnnnnnnn-3',wherein "Nf" stands for a 2'-fluoro modified nucleotide, and wherein "n" stands for a 2'-O-methyl modified nucleotide.
11. The polynucleic acid molecule of any one of claims 6-10, wherein the modified internucleotide linkage is a phosphorothioate internucleotide linkage.
12. The polynucleic acid molecule of any one of claims 6-11, wherein the modified internucleotide linkage comprises a stereochemically enriched phosphorothioate internucleotide linkage.
13. The polynucleic acid molecule of any one of claims 1-12, 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: 325-432, 505-528, 547-552, and 586-596.

14. The polynucleic acid molecule of any one of claims 1-13, 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: 109-216, 457-480, 535-540, and 564-574.
15. The polynucleic acid molecule of any one of claims 1-14, wherein the sense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 325-432, 505-528, 547-552, and 586-596, and the antisense strand comprises a nucleic acid sequence selected from SEQ ID NOs: 109-216, 457-480, 535-540, and 564-574.
16. A polynucleic acid molecule for modulating expression of apolipoprotein C3 (*APOC3*) gene, wherein polynucleic acid molecule comprises:
- (a) an antisense strand comprising the nucleotide sequence of UUUCAGGGAACUGAAGCCAUCGG (SEQ ID NO:529) and a sense strand comprising the nucleotide sequence of GAUGGCUUCAGUUCCCUGAAA (SEQ ID NO:541);
 - (b) an antisense strand comprising the nucleotide sequence of UGAAUACUGUCCCUUUUAAGCAA (SEQ ID NO:530) and a sense strand comprising the nucleotide sequence of GCUUAAAAGGGACAGUAUUCA (SEQ ID NO:542);
 - (c) an antisense strand comprising the nucleotide sequence of UAGAAUACUGUCCCUUUUAAGCA (SEQ ID NO:531) and a sense strand comprising the nucleotide sequence of CUUAAAAGGGACAGUAUUCUA (SEQ ID NO:543);
 - (d) an antisense strand comprising the nucleotide sequence of UUGAGAAUACUGUCCCUUUUAAG (SEQ ID NO:532) and a sense strand comprising the nucleotide sequence of UAAAAGGGACAGUAUUCUCAA (SEQ ID NO:544);
 - (e) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO:533) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO:545);
 - (f) an antisense strand comprising the nucleotide sequence of UCACUGAGAAUACUGUCCCUUUU (SEQ ID NO:534) and a sense strand comprising the nucleotide sequence of AAGGGACAGUAUUCUCAGUGA (SEQ ID NO:546);

- (g) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 554) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 576);
- (h) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUCAA (SEQ ID NO: 555) and a sense strand comprising the nucleotide sequence of GAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 577);
- (i) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUGAA (SEQ ID NO: 556) and a sense strand comprising the nucleotide sequence of CAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 578);
- (j) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUGCAA (SEQ ID NO: 557) and a sense strand comprising the nucleotide sequence of GCAAGGGACAGUAUUCUCAGA (SEQ ID NO: 579);
- (k) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUCGAA (SEQ ID NO: 558) and a sense strand comprising the nucleotide sequence of CGAAGGGACAGUAUUCUCAGA (SEQ ID NO: 580);
- (l) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 559) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 581);
- (m) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUGAA (SEQ ID NO: 560) and a sense strand comprising the nucleotide sequence of CAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 582);
- (n) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 561) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 583);
- (o) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 562) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 584); or

(p) an antisense strand comprising the nucleotide sequence of UCUGAGAAUACUGUCCCUUUUAA (SEQ ID NO: 563) and a sense strand comprising the nucleotide sequence of AAAAGGGACAGUAUUCUCAGA (SEQ ID NO: 585).

17. A polynucleic acid molecule for modulating expression of apolipoprotein C3 (*APOC3*) gene, wherein polynucleic acid molecule comprises:

(a) an antisense strand comprising the nucleotide sequence of usUfsucagGfgaacUfgAfaGfccaucsgsg (SEQ ID NO:535) and a sense strand comprising the nucleotide sequence of gsauggcUfuCfaGfuucccugaaa (SEQ ID NO:547);

(b) an antisense strand comprising the nucleotide sequence of usGfsaauCfugucCfcUfuUfuaagsasa (SEQ ID NO:536) and a sense strand comprising the nucleotide sequence of gscsuuaaAfaGfgGfacaguuuca (SEQ ID NO:548);

(c) an antisense strand comprising the nucleotide sequence of usAfsgaauAfcuguCfcCfuUfuaagsasa (SEQ ID NO:537) and a sense strand comprising the nucleotide sequence of csusuuaaAfgGfgAfcaguuucua (SEQ ID NO:549);

(d) an antisense strand comprising the nucleotide sequence of usUfsgagaAfuacuGfuCfcCfuuuuasag (SEQ ID NO:538) and a sense strand comprising the nucleotide sequence of usasaaagGfgAfcAfguuucucua (SEQ ID NO:550);

(e) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO:539) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO:551);

(f) an antisense strand comprising the nucleotide sequence of usCfsacugAfgaauAfcUfgUfcccususu (SEQ ID NO:540) and a sense strand comprising the nucleotide sequence of asasgggaCfaGfuAfuucucaguga (SEQ ID NO:552);

(g) an antisense strand comprising the nucleotide sequence of vpusCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO: 565) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 587);

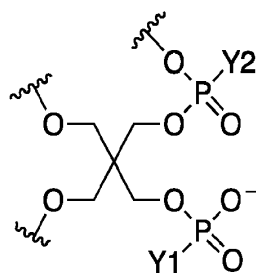
(h) an antisense strand comprising the nucleotide sequence of usCfsugagAfauacUfgUfcCfcuuusasa (SEQ ID NO: 566) and a sense strand comprising the nucleotide sequence of gsasaaggGfaCfaGfuauucucaga (SEQ ID NO: 588);

- (i) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuugsasa (SEQ ID NO: 567) and a sense strand comprising the nucleotide sequence of csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 589);
- (j) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuugcsasa (SEQ ID NO: 568) and a sense strand comprising the nucleotide sequence of gscsaaggGfaCfaGfuauucucaga (SEQ ID NO: 590);
- (k) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuugcsasa (SEQ ID NO: 569) and a sense strand comprising the nucleotide sequence of csgsaaggGfaCfaGfuauucucaga (SEQ ID NO: 591);
- (l) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuusasa (SEQ ID NO: 570) and a sense strand comprising the nucleotide sequence of (invAb)asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 592);
- (m) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuugsasa (SEQ ID NO: 571) and a sense strand comprising the nucleotide sequence of (invAb)csasaaggGfaCfaGfuauucucaga (SEQ ID NO: 593);
- (n) an antisense strand comprising the nucleotide sequence of usCfsugdAgdAauacUfgUfcCfcuuusasa (SEQ ID NO: 572) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 594);
- (o) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfscCfcuuusasa (SEQ ID NO: 573) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 595); or
- (p) an antisense strand comprising the nucleotide sequence of usCfsugagAfaucUfgUfcCfcuuusasa (SEQ ID NO: 574) and a sense strand comprising the nucleotide sequence of asasaaggGfaCfaGfuauucucaga (SEQ ID NO: 596),

wherein “A” refers to adenosine-3’-phosphate; “a” refers to 2’-O-methyladenosine-3’-phosphate; “Af” refers to 2’-fluoroadenosine-3’-phosphate; “dA” refers to 2’-deoxyadenosine-3’-phosphate; “C” refers to cytidine-3’-phosphate; “c” refers to 2’-O-methylcytidine-3’-phosphate; “Cf” refers to 2’-fluorocytidine-3’-phosphate; “dC” refers to 2’-deoxycytidine-3’-phosphate; “G” refers to guanosine-3’-phosphate; “g” refers to 2’-O-methylguanosine-3’-phosphate; “Gf” refers to 2’-fluoroguanosine-3’-phosphate; “dG” refers to 2’-deoxyguanosine-

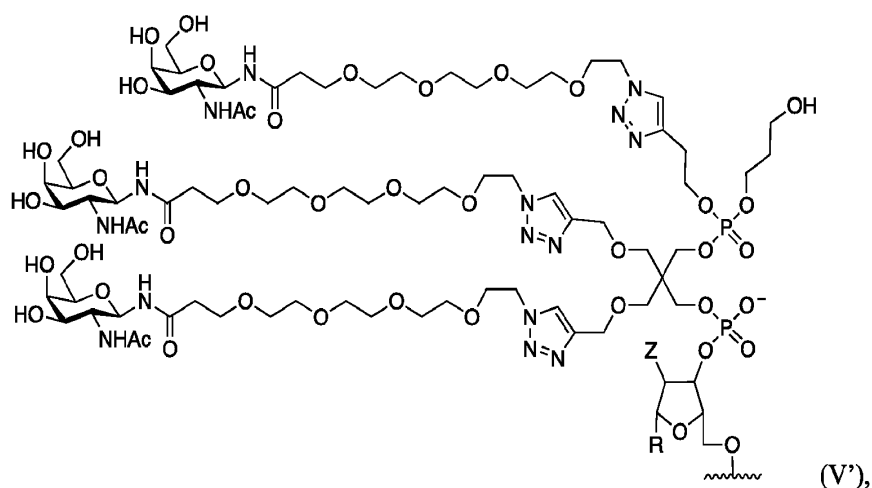
3'-phosphate; "U" refers to uridine-3'-phosphate; "u" refers to 2'-O-methyluridine-3'-phosphate; "Uf" refers to 2'-fluorouridine-3'-phosphate; "T" refers to 5-methyluridine-3'-phosphate; "t" refers to 2'-O-methyl-5-methyluridine-3'-phosphate; "Tf" refers to 2'-fluoro-5-methyluridine-3'-phosphate; "dT" refers to 2'-deoxythymidine-3'-phosphate; "s" refers to 3'-phosphorothioate, "(invAb)" refers to inverted abasic deoxyribonucleotide, and "vp" refers to 5'-vinylphosphonate modified nucleotide.

18. A polynucleic acid molecule conjugate for modulating expression of apolipoprotein C3 (*APOC3*) gene, wherein the polynucleic acid molecule conjugate comprises a polynucleic acid molecule of any one of claims 1-17 and an asialoglycoprotein receptor targeting moiety.
19. The polynucleic acid molecule conjugate of claim 18, wherein the asialoglycoprotein receptor targeting moiety comprises N-Acetylgalactosamine (GalNAc) or galactose.
20. The polynucleic acid molecule conjugate of claim 18 or 19, wherein the polynucleic acid molecule and the asialoglycoprotein receptor targeting moiety is coupled via a linker.
21. The polynucleic acid molecule conjugate of claim 20, wherein the linker comprises formula (IV) below,

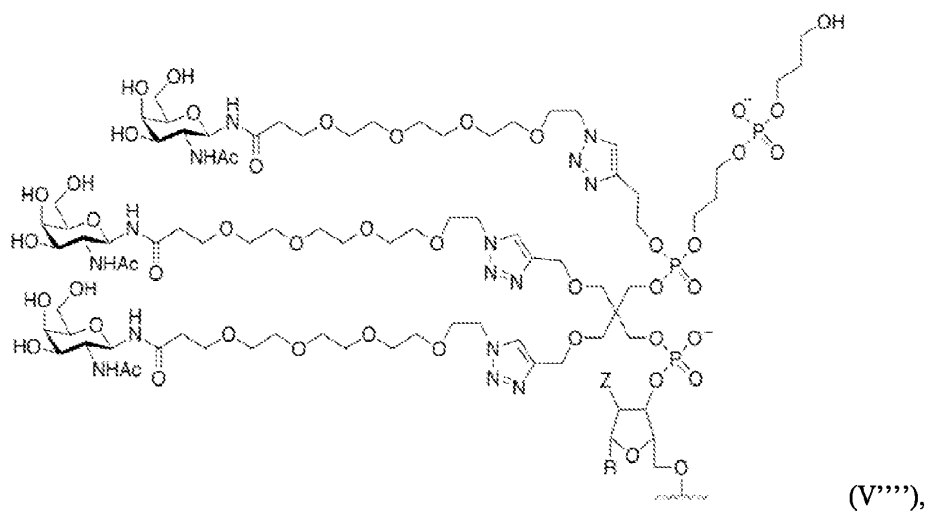


, wherein at least one of Y1 and Y2 is a nucleotide in the polynucleic acid molecule.

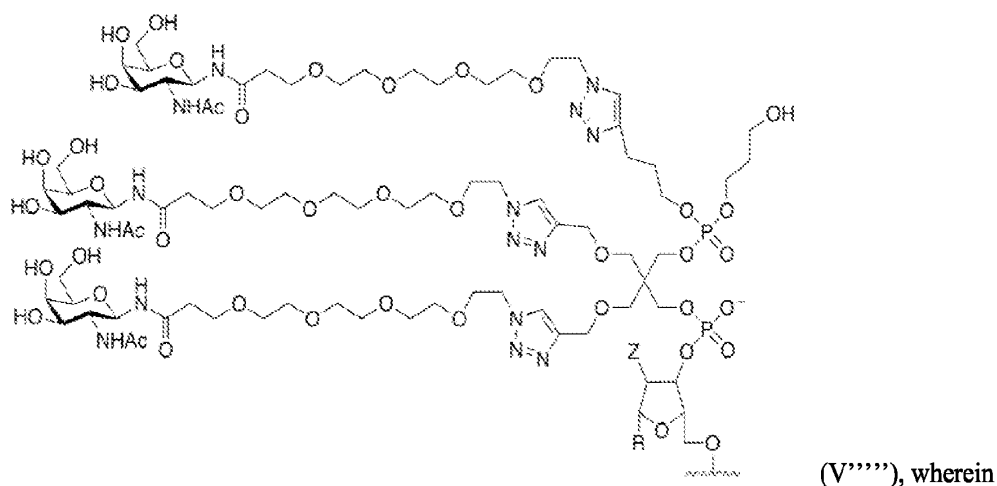
22. The polynucleic acid molecule conjugate of claim 21, wherein the Y1 is the last nucleotide on the 3'-terminus of the sense strand of the polynucleic acid molecule or the Y1 and Y2 are two consecutive nucleotides in the polynucleic acid molecule.
23. The polynucleic acid molecule conjugate of any one of claims 20-22, 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'''), (V'''''), or (V'''''):



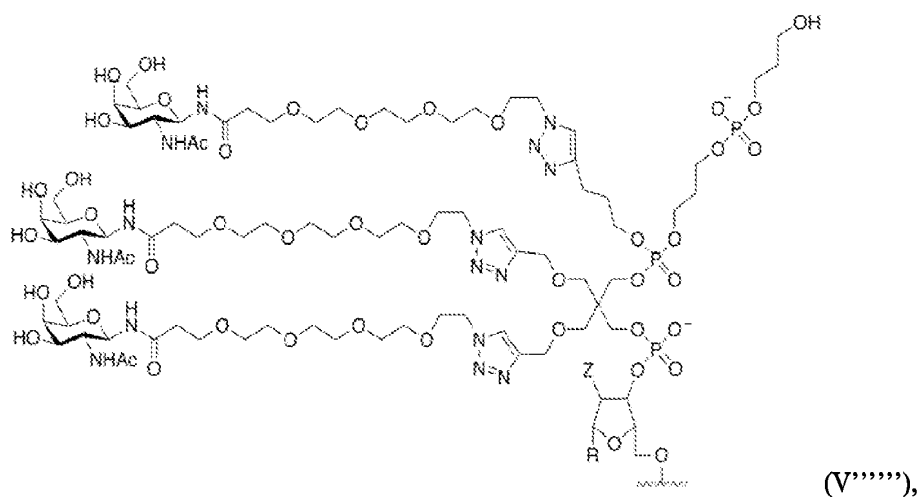
wherein Z in formula (V') is -H, -OH, -O-Methyl, -F, or -O-methoxyethyl, and R in formula (V') is adenine, uracil, guanine, cytosine, thymine, abasic, or others;



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;

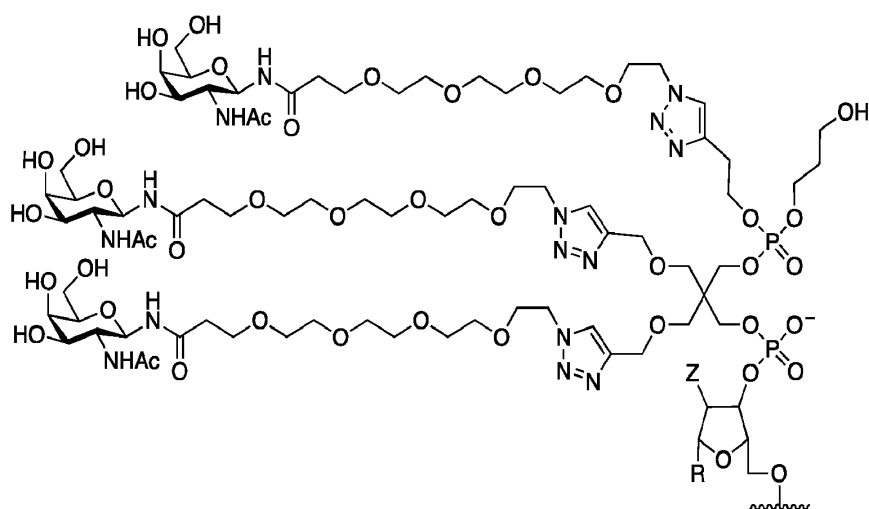


Z in formula (V''''') is a moiety that corresponds to one of the sugar modifications described herein (e.g., -H, -OH, -O-Methyl, -F, or -O-methoxyethyl) and R in formula (V''''') is adenine, uracil, guanine, cytosine, thymine, abasic, or others;



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.

24. The polynucleic acid molecule conjugate of claim 23, 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.

25. A pharmaceutical composition comprising a polynucleic acid molecule of any one of claims 1-17 or a polynucleic acid molecule conjugate of any one of claims 18-24, and a pharmaceutically acceptable excipient.
26. The pharmaceutical composition of claim 25, wherein the pharmaceutical composition is formulated as a nanoparticle formulation.
27. The pharmaceutical composition of claim 25 or 26, wherein the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.
28. A method of modulating expression of apolipoprotein C3 (*APOC3*) gene in a subject in need thereof, comprising: administering to the subject a polynucleic acid molecule of any one of claims 1-17 or a polynucleic acid molecule conjugate of any one of claims 18-24, or a pharmaceutical composition of any one of claims 25-27, thereby modulating the expression of *APOC3* gene in the subject.
29. A method of modulating triglyceride level in a subject in need thereof, comprising: administering to the subject a polynucleic acid molecule of any one of claims 1-17 or a polynucleic acid molecule conjugate of any one of claims 18-24, or a pharmaceutical composition of any one of claims 25-27, thereby modulating triglyceride level in the subject.

30. The method of claim 28 or 29, wherein the subject in need thereof is diagnosed of, suffers from, or having a symptom of cardiovascular disease or hypertriglyceridemia.