

COMPOSITIONS AND METHODS FOR MODULATING APOC3 EXPRESSION

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims the priority of US provisional application number 63/264,730, filed December 1, 2021, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[002] A Sequence Listing conforming to the rules of WIPO Standard ST.26 is hereby incorporated by reference in its entirety. The Sequence Listing has been filed as an electronic document via EFS-Web in ASCII format encoded as XML. The electronic document, created on November 29, 2022, is entitled "400930-032WO-194344_ST26.xml," and is 2,599,277 bytes in size.

TECHNICAL FIELD

[003] The disclosure relates generally to biology and medicine, and more particularly it relates to oligonucleotide composition and their use for inhibiting or reducing apolipoprotein C-III (*APOC3*) gene expression, as well as their use for treating diseases, disorders and/or conditions associated with *APOC3*.

BACKGROUND

[004] *APOC3* is a protein encoded by *APOC3*, is a protein found on triglyceride-rich lipoproteins (TRLs) and high-density lipoprotein (HDL) having inhibitory activity toward lipoprotein lipase (LPL) and hepatic lipase (HL) and is a protein that delays hepatic clearance of TRLs. Human *APOC3* is expressed highly in hepatocytes and in the small intestine.

[005] Several naturally occurring gain-of-function polymorphisms have been identified in the *APOC3* gene, which are postulated to be contributing factors in development of hypertriglyceridemia. These polymorphisms are strongly associated with a wide spectrum of diseases, such as non-alcoholic fatty liver disease (NAFLD), metabolic syndromes (MetS), insulin resistance, acute coronary diseases (ACD), and coronary heart diseases (CHD) resulting from hypertriglyceridemia. Several loss-of-function polymorphisms have been shown to be associated with reduced plasma triglycerides and liver fat, increased plasma concentration of HDL cholesterol and APOA1, and reduction of risks of ischemic artery and heart disease and coronary artery diseases.

[006] Several RNA-based therapeutics are known that can inhibit or reduce *APOC3* expression. For example, Intl. Patent Application Publication Nos. WO 2010/083615, WO 2012/177947, WO 2016/011123, WO 2016/081444, and WO 2019/051402, as well as CN Patent Application Publication No. 108239644, describe double-stranded (ds) RNAi constructs for inhibiting or reducing *APOC3* expression, as well as methods of using the same for treating or preventing lipid metabolism conditions, diseases and/or disorders such as obesity and cardiometabolic disorders. Also, Intl. Patent Application Publication No. WO 2014/205451 describes antisense oligonucleotides for inhibiting or reducing *APOC3* expression.

[007] Despite the existence of some therapeutics directed toward *APOC3*, there is a need for additional therapeutics for inhibiting or reducing *APOC3* expression for treating liver disease.

BRIEF SUMMARY

[008] To address this need, the disclosure describes compositions and methods for treating a disease, disorder, and/or condition related to *APOC3* expression. The disclosure is based, in part, on discovering and developing ds oligonucleotides (*e.g.*, RNAi oligonucleotides) for selectively inhibiting and/or reducing *APOC3* expression in, for example, the liver. Accordingly, target sequences within *APOC3* have been identified, and RNAi oligonucleotides that bind to these target sequences and inhibit *APOC3* mRNA expression have been generated. As shown herein, the RNAi oligonucleotides inhibit human and non-human primate (NHP) *APOC3* expression in the liver. Without being bound by theory, the RNAi oligonucleotides herein are useful for treating a disease, disorder or condition associated with *APOC3* expression (*e.g.*, hypertriglyceridemia or another dyslipidemia). In general, the RNAi oligonucleotides herein are useful for treating a disease, disorder, or condition associated with aberrant *APOC3* expression (*e.g.*, *APOC3* gain-of-function polymorphisms). In particular, the RNAi oligonucleotides herein are useful for treating a disease, disorder, or condition associated with mutant *APOC3* expression.

[009] Accordingly, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *APOC3* expression that include a sense strand and/or an antisense strand, where the sense strand has a sequence as set forth in Table 2, and where the antisense strand has a sequence as set forth in Table 2.

[0010] In some embodiments, the sense strand has a sequence as set forth in Table 2 (*e.g.*, any one of the odd numbers of SEQ ID NOs:9 to 170), especially any one of SEQ ID NOs:37, 43, 45, 87, 89, 99, 101, and 105.

[0011] In some embodiments, the antisense strand having a sequence as set forth in Table 2 (*e.g.*, any one of the even numbers of SEQ ID NOs:9 to 170), especially any one of SEQ ID NOs:38, 44, 46, 88, 90, 100, 102, and 106.

[0012] Alternatively, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *APOC3* expression that include a sense strand and/or an antisense strand, where the sense strand has a sequence as set forth in Table 3, and where the antisense strand has a sequence as set forth in Table 3.

[0013] In some embodiments, the sense strand has a sequence as set forth in Table 3 (*e.g.*, any one of the odd numbers of SEQ ID NOs:171 to 332), especially any one of SEQ ID NOs:199, 205, 207, 249, 251, 261, 263, and 267.

[0014] In some embodiments, the antisense strand has a sequence as set forth in Table 3 (*e.g.*, any one of the even numbers of SEQ ID NOs:171 to 332), especially any one of SEQ ID NOs:200, 206, 208, 250, 252, 262, 264, and 268.

[0015] Alternatively, RNAi oligonucleotides are described for reducing or inhibiting *APOC3* expression that include a sense strand and an antisense strand, where the sense and antisense strands form a duplex region, and where the antisense strand has a region of complementarity to a *APOC3* mRNA target sequence of any one of SEQ ID NOs:334 to 341.

[0016] In any of the embodiments above, the sense strand is from about 15 nucleotides to about 50 nucleotides in length. In some embodiments, the sense strand is from about 20 nucleotides to about 40 nucleotides in length. In some embodiments, the sense strand is 36 nucleotides in length.

[0017] In any of the embodiments above, the antisense strand is from about 15 nucleotides to about 30 nucleotides in length. In some embodiments, the antisense strand is from about 20 nucleotides to about 25 nucleotides. In some embodiments, the antisense strand is 22 nucleotides in length.

[0018] In any of the embodiments above, the duplex region is from about 19 nucleotides in length to about 21 nucleotides in length. In certain embodiment, the duplex region is 20 nucleotides in length.

[0019] In any of the embodiments above, the region of complementarity is at least 15 contiguous nucleotides in length. In some embodiments, the region of complementarity is from

about 19 contiguous nucleotides in length to about 21 contiguous nucleotides in length. In other embodiments, the region of complementarity is 19 contiguous nucleotides in length, 20 contiguous nucleotides in length, or 21 contiguous nucleotides in length.

[0020] In any of the embodiments above, the RNAi oligonucleotides include on the sense strand a 3' end a stem-loop set forth as: S1-L-S2, where S1 is complementary to S2, and where L forms a loop between S1 and S2 of about 3 to about 5 nucleotides in length.

[0021] In any of the embodiments above, the antisense strand, the sense strand, or both have an overhang sequence. In some embodiments, the antisense strand includes a 3'-overhang of 1 or more nucleotides in length. In other embodiments, the 3'-overhang sequence is 2 nucleotides in length such as, for example, GG.

[0022] Oligonucleotides also are described that include an antisense strand and a sense strand, where the antisense strand can be from about 21 nucleotides to about 27 nucleotides in length and has a region of complementarity to *APOC3*, wherein the sense strand includes a stem-loop at its 3' end set forth as: S1-L-S2, wherein S1 is complementary to S2, wherein L forms a loop between S1 and S2 from about 3 nucleotides to about 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least about 19 nucleotides in length but are not covalently linked.

[0023] In some embodiments, the loop L is a triloop (triL) or a tetraloop (L). In some embodiments, L is a tetraloop of 4 nucleotides in length. In other embodiments, L includes a sequence 5'-GAAA-3'.

[0024] In some embodiments, S1 and S2 are 1-10 nucleotides in length and have the same length. In other embodiments, S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length. In other embodiments, S1 and S2 are 6 nucleotides in length. In certain embodiments, the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:333).

[0025] In some embodiments, the sense strand is 25 nucleotides in length and the antisense strand is 27 nucleotides in length. In other embodiments, the sense strand is 36 nucleotides in length and the antisense strand is 22 nucleotides in length.

[0026] In the embodiments above, the duplex region includes a 3'-overhang sequence on the antisense strand. In some embodiments, the 3'-overhang sequence on the antisense strand is 2 nucleotides in length.

[0027] In any of the embodiments above, at least one nucleotide in an oligonucleotide is a modified nucleotide. In some embodiments, all nucleotides in the oligonucleotide are modified except for nucleotides in the stem-loop (*i.e.*, S1-L-S2). In other embodiments, all nucleotides in the oligonucleotide are modified except for nucleotides in the loop (*i.e.*, L).

[0028] In some embodiments, the modified nucleotide includes a 2'-modification such as, for example, 2'-aminoethyl (EA), 2'-fluoro (2'-F), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE) and 2'-deoxy-2'-fluoro- β -arabinonucleic acid (2'-FANA). In certain embodiments, all nucleotides in an oligonucleotide include a 2'-modification such as, for example, 2'-F or 2'-OMe.

[0029] In any of the embodiments above, at least one nucleotide in an oligonucleotide includes a modified internucleotide linkage. In some embodiments, the modified internucleotide linkage is a phosphorothioate linkage.

[0030] In any of the embodiments above, a 4'-carbon of a sugar of a 5'-nucleotide of the antisense strand includes a phosphate analog such as, for example, an oxymethylphosphonate, vinylphosphonate or malonyl phosphonate. Alternatively, or optionally, the phosphate analog is a 4'-phosphate analog including 5'-methoxyphosphonate-4'-oxy.

[0031] In any of the embodiments above, at least one nucleotide of an oligonucleotide can be conjugated to one or more targeting ligands such as, for example, an amino sugar, carbohydrate, cholesterol, lipid, or polypeptide. In some embodiments, the targeting ligand is a N-acetylgalactosamine (GalNAc) moiety. In other embodiments, the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

[0032] In some embodiments, the targeting ligands are conjugated to one or more nucleotides of L of the stem loop. In certain embodiments, up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

[0033] In certain embodiments, one or more nucleotides at positions 8, 9, 10, or 11 of the sense strand are modified with a 2'-F. In other embodiments, the sugar moiety at each nucleotide at positions 1 to 7, 12 to 27 and 31 to 36 in the sense strand is modified with a 2'-OMe. In certain embodiments, nucleotides at positions 8 to 11 of the sense strand are modified with a 2'-F, and positions 1 to 7, 12 to 27 and 31 to 36 are modified with a 2'-OMe.

[0034] In certain other embodiments, the sense strand includes a 2'-F modified nucleotide at positions 8 to 11, a 2'-OMe modified nucleotide at positions 1 to 7, 12 to 27 and 31 to 36, a

GalNAc-conjugated nucleotide at position 28, 29 and 30, and a phosphorothioate linkage between positions 1 and 2.

[0035] In certain other embodiments, one or more nucleotides at positions 2 to 5, 7, 10 and 14 of the antisense strand are modified with 2'-F, and one or more nucleotides at positions 1, 6, 8-9, 11-13 and 15-22 modified with a 2'-OMe. In other embodiments, the antisense strand includes a 2'-F-modified nucleotide at positions 2 to 5, 7, 10 and 14, and a 2'-OMe-modified nucleotide at positions 1, 6, 8 to 9, 11 to 13 and 15 to 22.

[0036] In certain embodiments, the antisense strand includes a 2'-F modified nucleotide at positions 2 to 5, 7, 10 and 14, a 2'-OMe at positions 1, 6, 8 to 9, 11 to 13 and 15 to 22, and a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, positions 3 and 4, positions 20 and 21, and positions 21 and 22.

[0037] In certain embodiments, the oligonucleotides have a modification pattern as shown in FIG. 1A, 1B or 1C.

[0038] FIG. 1A depicts modification pattern 1, wherein the modification pattern of each strand is illustrated below:

Sense Strand: 5' mX-S-mX-fX-mX-mX-mX-mX-fX-fX-fX-mX-fX-fX-mX-mX-mX-fX-mX-mX-mX-mX-mX-mX-mX-mX-[X-GalNAc]-[X-GalNAc]-[X-GalNAc]-[X-GalNAc]-mX-mX-mX-mX-mX-mX 3'

Hybridized to:

Antisense Strand: 5' [MePhosphonate-4O-mX]-S-fX-S-fX-S-mX-fX-mX-fX-fX-mX-fX-mX-fX-mX-fX-mX-mX-fX-mX-S-mX-S-mX 3';

or represented as follows:

Sense Strand: 5' [mXs][mX][fX][mX][mX][mX][mX][fX][fX][fX][mX][fX][fX][mX][mX][fX][mX][mX][mX][mX][mX][mX][X-GalNAc][X-GalNAc][X-GalNAc][X-GalNAc][mX][mX][mX][mX][mX] 3'

Hybridized to:

Antisense Strand: 5' [MePhosphonate-4O-mX]-S-fX-S-fX-S-mX-fX-mX-fX-mX-mX-fX-mX-fX-mX-fX-mX-fX-mX-fX-mX-S-mX-S-mX 3';

or represented as follows:

Sense Strand: 5' [mXs][mX][fX][mX][fX][mX][mX][fX][fX][fX][mX][fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mX][X-GalNAc][X-GalNAc][X-GalNAc][X-GalNAc][mX][mX][mX][mX][mX][mX] 3'

Hybridized to:

Antisense Strand: 5' [MePhosphonate-4O-mXs][fXs][fXs][mX][fX][mX][fX][mX][mX][fX][mX][fX][mX][fX][mX][fX][mX][fX][mXs][mXs][mX] 3'.

Modification key for the modification patterns 1-3 above:

Symbol	Modification/linkage
Key 1	
mX	2'-O-methyl modified nucleotide
fX	2'- fluoro modified nucleotide
-S-	phosphorothioate linkage
-	phosphodiester linkage
[MePhosphonate-4O-mX]	5'-methoxyphosphonate-4'-oxy modified nucleotide
X-GalNAc	ademX-GalNAc or prgX-peg-GalNAc
Key 2	
[mXs]	2'-O-methyl modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[fXs]	2'- fluoro modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[mX]	2'-O-methyl modified nucleotide with phosphodiester linkages to neighboring nucleotides
[fX]	2'- fluoro modified nucleotide with phosphodiester linkages to neighboring nucleotides

[0041] In any of the embodiments above, the oligonucleotide is a RNAi oligonucleotide. In some embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence as set forth in Table 2, especially any one of SEQ ID NOs:37, 43, 45, 87, 89, 99, 101, and 105. In certain embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence as set forth in Table 3, especially any one of SEQ ID NOs:199, 205, 207,

249, 251, 261, 263, and 267. In some embodiments, the RNAi oligonucleotide includes an antisense strand having a nucleotide sequence as set for the in Table 2, especially any one of SEQ ID NOs:38, 44, 46, 88, 90, 100, 102, and 106. In certain embodiments, the RNAi oligonucleotide includes an antisense strand having a nucleotide sequence as set forth the in Table 3, especially any one of SEQ ID NOs:200, 206, 208, 250, 252, 262, 264, and 268.

[0042] In certain embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs:37, 43, 45, 87, 89, 99, 101 and 105, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs:38, 44, 46, 88, 90, 100, 102 and 106.

[0043] In certain embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs:37, 89 and 101, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs:38, 90 and 102.

[0044] In certain other embodiments, the sense strand, and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

- (a) SEQ ID NOs:37 and 38,
- (b) SEQ ID NOs:43 and 44,
- (c) SEQ ID NOs:45 and 46,
- (d) SEQ ID NOs:87 and 88,
- (e) SEQ ID NOs:89 and 90,
- (f) SEQ ID NOs:99 and 100,
- (g) SEQ ID NOs:101 and 102, and
- (h) SEQ ID NOs:105 and 106.

[0045] In certain embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs:199, 205, 207, 249, 251, 261, 263, and 267, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs:200, 206, 208, 250, 252, 262, 264, and 268.

[0046] In certain embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs:199, 251 and 263, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs:200, 252 and 264.

[0047] In certain other embodiments, the sense strand, and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

- (a') SEQ ID NOs:199 and 200,
- (b') SEQ ID NOs:205 and 206,

- (c') SEQ ID NOs:207 and 208,
- (d') SEQ ID NOs:249 and 250,
- (e') SEQ ID NOs:251 and 252,
- (f') SEQ ID NOs:261 and 262,
- (g') SEQ ID NOs:263 and 264, and
- (h') SEQ ID NOs:267 and 268.

[0048] Oligonucleotides also are described for inhibiting or reducing *APOC3* expression that include a sense strand and an antisense strand, where the sense strand and the antisense strand form a duplex region, where all nucleotides of the sense strand and the antisense strand include a modification of a base, a sugar and/or an internucleotide linkage, where the antisense strand includes a region of complementarity to a *APOC3* mRNA target sequence of one of SEQ ID NOs:334 to 341, and where the region of complementarity is at least about 15 contiguous nucleotides in length.

[0049] In other aspects, pharmaceutical compositions are described that include at least one oligonucleotide herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, delivery agent or excipient. In some embodiments, the pharmaceutical compositions include an additional therapeutic agent such as, for example, a lipid-lowering agent, an antidiabetic agent, or anti-obesity agent.

[0050] In other aspects, methods are described for reducing *APOC3* expression in a cell, a population of cells, a tissue, an organ, or an individual that include at least a step of administering/contacting the cell, the population of cells, the tissue, the organ, or the individual with an oligonucleotide herein or a pharmaceutical composition herein. In some embodiments, reducing *APOC3* expression includes reducing an amount or level of *APOC3* mRNA, an amount or level of *APOC3* protein, or both in the cell, the population of cells, the tissue, the organ, or the individual. In some embodiments, the cell, the cell population, the tissue, the organ, or the individual has a disease, disorder, or condition associated with *APOC3* expression. In certain embodiments, the disease, disorder, or condition associated with *APOC3* expression is hypertriglyceridemia, high non-HDL cholesterol, liver steatosis, insulin resistance or even atherosclerotic cardiovascular disease (ASCVD).

[0051] In other aspects, methods are described for treating an individual having or suspected of having a disease, disorder or condition associated with *APOC3* expression. The methods include at least a step of administering to an individual in need thereof an effective amount of an oligonucleotide herein or a pharmaceutical composition herein. In some embodiments, the

disease, disorder, or condition associated with *APOC3* expression is hypertriglyceridemia, high non-HDL cholesterol, liver steatosis, insulin resistance or even ASCVD. In some embodiments, the oligonucleotide or pharmaceutical composition is administered daily, weekly, monthly, quarterly, yearly *via* subcutaneous (SQ) administration, especially monthly or quarterly.

[0052] In some embodiments, the individual has NAFLD, liver steatosis, non-alcoholic steatohepatitis (NASH), alcoholic hepatitis (AH), alcoholic liver disease (ALD), cholangiocarcinoma (CCA), cirrhosis, , hepatic fibrosis, hepatic inflammation, hepatocellular carcinoma (HCC), primary sclerosing cholangitis (PSC), hyperlipidemia, diabetes, and /or obesity.

[0053] In any of the embodiments above, the methods may comprise additional steps such as measuring or obtaining genotype information, *APOC3* expression, APOC3 protein levels, the individual's weight and/or blood glucose and/or cholesterol and/or LPL and/or TG and then comparing such obtained values to one or more baseline values or previously obtained values to assess the effectiveness of contacting or administering. In some embodiments, the additional step comprises confirming that the individual has an *APOC3* gain-of-function polymorphism. In some embodiments, the additional step comprises confirming that the individual has a single-nucleotide polymorphism (SNP) of rs5128, rs2854116, rs2854117, rs2070666, or mutation of 1100C>T, 2845T>G or Gln38Lys.

[0054] In any of the embodiments above, the methods can include administering the RNAi oligonucleotide or pharmaceutical composition simultaneously, separately, or sequentially with a second composition or a second therapeutic agent. In some embodiments, the second composition or a second therapeutic agent is a APOC3 antibody or fragment thereof, a lipid-lowering agent, an antidiabetic agent or anti-obesity agent. In some embodiments, the second composition or second therapeutic agent is administered with a frequency same as the RNAi oligonucleotide (*i.e.*, every other day, twice a week, or even weekly). In other embodiments, the second composition or second therapeutic agent is administered with a frequency distinct from the RNAi oligonucleotide. Likewise, in other embodiments, the second composition or second therapeutic agent is administered *via* the same route as the RNAi oligonucleotide (*e.g.*, SQ). In still other embodiments, the second composition or second therapeutic agent is administered *via* a route that differs from the RNAi oligonucleotide).

[0055] In other aspects, uses are described for the RNAi oligonucleotides herein for treating a disease, disorder or condition associated with *APOC3* expression, which optionally are

administered simultaneously, separately, or sequentially (*i.e.*, in combination) with a second composition or second therapeutic agent.

[0056] In other aspects, uses are described for the RNAi oligonucleotides herein in manufacturing a medicament for treating a disease, disorder, or condition associated with *APOC3* expression, where the medicament optionally further includes a second composition or second therapeutic agent.

[0057] In other aspects, kits are described that include at least one oligonucleotide herein, an optional pharmaceutically acceptable carrier, and a package insert having instructions for administering the same to an individual having a disease, disorder, or condition associated with *APOC3* expression.

[0058] An advantage of the oligonucleotides and compositions herein is that suppressed *APOC3* expression exerts a beneficial effect on the entire spectrum of dyslipidemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0059] The advantages, effects, features, and objects other than those set forth above will become more readily apparent when consideration is given to the detailed description below. Such detailed description refers to the following drawing(s), where:

[0060] FIGS. 1A-1C disclose schematics depicting the structure and chemical modification pattern for 3 generic GalNAc-conjugated *APOC3* oligonucleotides (M1, M2 and M3, respectively).

DETAILED DESCRIPTION

Overview

[0061] Dyslipidemia refers to unhealthy levels of one or more kinds of lipid (fat) in blood. There are three main types of lipids: high-density lipoprotein (HDL), low-density lipoprotein (LDL), and TGs. Dyslipidemia is divided up into primary and secondary types. Primary dyslipidemia is inherited, whereas secondary dyslipidemia is an acquired condition (*i.e.*, develops from other causes such as, for example, obesity or diabetes).

[0062] RNA interference (RNAi) is a process of introducing exogenous RNA into a cell leading to specific degradation of the mRNA encoding the targeted protein with a resultant decrease in target gene expression.

[0063] In humans, *APOC3* is 99 amino acids in length (residues 1-20, however, are a signal peptide that is subsequently cleaved) with a predicted molecular weight of 8.8 kDa. Exemplary

nucleic acid sequences for *APOC3* can found in GenBank Reference Sequence Number NM_000040 (human), GenBank Reference Sequence Number NM_001289755 (mouse), GenBank Reference Sequence Number NM_001271053 (rat), GenBank Reference Sequence Number XM_005579730 (NHP), GenBank Reference Sequence Number XM_001090312 (NHP), GenBank Reference Sequence Number XM_008020977 (NHP), and GenBank Reference Sequence Number XM_035264642 (NHP). One of skill in the art, however, understands that additional examples of *APOC3* nucleic acid sequences are readily available using publicly available databases such as, for example, GenBank and UniProt.

Definitions

[0064] As used herein, “about” means within a statistically meaningful range of a value or values such as, for example, a stated concentration, length, molecular weight, pH, sequence similarity, time frame, temperature, volume, *etc.* Such a value or range can be within an order of magnitude typically within 20%, more typically within 10%, and even more typically within 5% of a given value or range. The allowable variation encompassed by “about” will depend upon the system under study, and can be readily appreciated by one of skill in the art.

[0065] As used herein, “administer,” “administering,” “administration” and the like refers to providing a substance (*e.g.*, an oligonucleotide herein or a composition herein) to an individual in a manner that is pharmacologically useful (*e.g.*, to treat a disease, disorder, or condition in the individual).

[0066] As used herein, “antisense strand” means an oligonucleotide herein that is complimentary to a region of a target sequence. Likewise, and as used herein, “sense strand” means an oligonucleotide herein that is complimentary to a region of an antisense strand.

[0067] As used herein, “*APOC3*” means the apolipoprotein C-III gene, which encodes a very low-density lipoprotein (VLDL) protein (*APOC3*) that inhibits lipoprotein lipase and hepatic lipase.

[0068] As used herein, “asialoglycoprotein receptor” or “ASGPR” means a bipartite C-type lectin formed by a major 48 kDa subunit (ASGPR-1) and minor 40 kDa subunit (ASGPR-2). ASGPR is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing of circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins).

[0069] As used herein, “attenuate,” “attenuating,” “attenuation” and the like refers to reducing or effectively halting. As a non-limiting example, one or more of the treatments herein

may reduce or effectively halt the onset or progression of AH, ACD, ALD, CCA, CHD, MetS, PSC, cirrhosis, hepatic fibrosis, hepatic inflammation, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual such as, for example, hyperlipidemia, diabetes and/or obesity. This attenuation may be exemplified by, for example, a decrease in one or more aspects (*e.g.*, symptoms, tissue characteristics, and cellular, inflammatory, or immunological activity, *etc.*) of AH, ACD, ALD, CCA, CHD, MetS, PSC, cirrhosis, hepatic fibrosis, hepatic inflammation, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual such as, for example, hyperlipidemia, diabetes and/or obesity; no detectable progression (worsening) of one or more aspects of AH, ACD, ALD, CCA, CHD, MetS, PSC, cirrhosis, hepatic fibrosis, hepatic inflammation, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual such as, for example, hyperlipidemia, diabetes and/or obesity; or no detectable aspects of AH, ACD, ALD, CCA, CHD, MetS, PSC, cirrhosis, hepatic fibrosis, hepatic inflammation, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual such as, for example, hyperlipidemia, diabetes and/or obesity in an individual when they might otherwise be expected.

[0070] As used herein, “attenuate,” “attenuating,” “attenuation” and the like means reducing or effectively halting. As a non-limiting example, one or more of the treatments herein may reduce or effectively halt the onset or progression of dyslipidemia/hypertriglyceridemia/hyperlipidemia in an individual. This attenuation may be exemplified by, for example, a decrease in one or more aspects (*e.g.*, symptoms, tissue characteristics, and cellular, inflammatory, or immunological activity, *etc.*) of AH, ACD, ALD, CCA, CHD, MetS, PSC, cirrhosis, hepatic fibrosis, hepatic inflammation, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual such as, for example, hyperlipidemia, diabetes and/or obesity in an individual when they might otherwise be expected.

[0071] As used herein, “complementary” means a structural relationship between two nucleotides (*e.g.*, on two opposing nucleic acids or on opposing regions of a single nucleic acid strand) that permits the two nucleotides to form base pairs with one another. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. Complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. Likewise, two nucleic acids may have regions

of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

[0072] As used herein, “contact,” “contacting” and the like means directly or indirectly introducing or delivering the RNAi into, for example, a cell by facilitating or effecting uptake or absorption into the cell.

[0073] As used herein, “deoxyribonucleotide” means a nucleotide having a hydrogen in place of a hydroxyl at the 2' position of its pentose sugar when compared with a ribonucleotide. A modified deoxyribonucleotide has one or more modifications substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the nucleobase, sugar, or phosphate group.

[0074] As used herein, “double-stranded oligonucleotide” or “ds oligonucleotide” means an oligonucleotide that is substantially in a duplex form. The complementary base-pairing of duplex region(s) of a ds oligonucleotide can be formed between antiparallel sequences of nucleotides of covalently separate nucleic acid strands. Likewise, complementary base-pairing of duplex region(s) of a ds oligonucleotide can be formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. Moreover, complementary base-pairing of duplex region(s) of a ds oligonucleotide can be formed from single nucleic acid strand that is folded (*e.g.*, *via* a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. A ds oligonucleotide can include two covalently separate nucleic acid strands that are fully duplexed with one another. However, a ds oligonucleotide can include two covalently separate nucleic acid strands that are partially duplexed (*e.g.*, having overhangs at one or both ends). A ds oligonucleotide can include an antiparallel sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

[0075] As used herein, “duplex,” in reference to nucleic acids (*e.g.*, oligonucleotides), means a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

[0076] As used herein, “excipient” means a non-therapeutic agent that may be included in a composition herein, for example, to provide or contribute to a desired consistency or stabilizing effect.

[0077] As used herein, “hepatocyte” or “hepatocytes” means cells of the parenchymal tissues of the liver. These cells make up about 70%-85% of the liver's mass and manufacture serum albumin, fibronectin (FBN) and the prothrombin group of clotting factors (except for Factors

3 and 4). Markers for hepatocyte lineage cells include, but are not limited to, transthyretin (Ttr), glutamine synthetase (Glul), hepatocyte nuclear factor 1a (Hnf1a) and hepatocyte nuclear factor 4a (Hnf4a). Markers for mature hepatocytes may include, but are not limited to, cytochrome P450 (Cyp3a11), fumarylacetoacetate hydrolase (Fah), glucose 6-phosphate (G6p), albumin (Alb) and OC2-2F8. *See, e.g., Huch et al. (2013) NATURE 494:247-50.*

[0078] As used herein, a “hepatotoxic agent” means a chemical compound, virus or other substance that is itself toxic to the liver or can be processed to form a metabolite that is toxic to the liver. Hepatotoxic agents may include, but are not limited to, carbon tetrachloride (CCl₄), acetaminophen (paracetamol), vinyl chloride, arsenic, chloroform, nonsteroidal anti-inflammatory drugs (such as aspirin and phenylbutazone).

[0079] As used herein, “labile linker” means a linker that can be cleaved (*e.g.*, by acidic pH). Likewise, “fairly stable linker” means a linker that cannot be cleaved.

[0080] As used herein, “liver inflammation” or “hepatitis” means a physical condition in which the liver becomes swollen, dysfunctional and/or painful, especially because of injury or infection, as may be caused by exposure to a hepatotoxic agent. Symptoms may include jaundice, fatigue, weakness, nausea, vomiting, appetite reduction and weight loss. Liver inflammation, if left untreated, may progress to fibrosis, cirrhosis, liver failure or liver cancer.

[0081] As used herein, “liver fibrosis,” “hepatic fibrosis” or “fibrosis of the liver” refers to an excessive accumulation in the liver of extracellular matrix proteins, which could include collagens (I, III, and IV), FBN, undulin, elastin, laminin, hyaluronan, and proteoglycans resulting from inflammation and liver cell death. Liver fibrosis, if left untreated, may progress to cirrhosis, liver failure or liver cancer.

[0082] As used herein, “loop” means an unpaired region of a nucleic acid (*e.g.*, oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cells), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a “stem”).

[0083] As used herein, “modified internucleotide linkage” means an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage having a phosphodiester bond. A modified nucleotide can be a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a

modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

[0084] As used herein, “modified nucleotide” refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide, and thymidine deoxyribonucleotide. A modified nucleotide can be a non-naturally occurring nucleotide. A modified nucleotide can have, for example, one or more chemical modification in its sugar, nucleobase, and/or phosphate group. Additionally, or alternatively, a modified nucleotide can have one or more chemical moieties conjugated to a corresponding reference nucleotide. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

[0085] As used herein, “nicked tetraloop structure” mean a structure of a RNAi oligonucleotide that is characterized by separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

[0086] As used herein, “nucleotide” means an organic molecule having a nucleoside (a nucleobase such as, for example, adenine, cytosine, guanine, thymine, or uracil; and a pentose sugar such as, for example, ribose or 2'-deoxyribose; and a phosphate group, which can serve as a monomeric unit of nucleic acid polymers such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

[0087] As used herein, “oligonucleotide” means a short nucleic acid molecule (*e.g.*, less than about 100 nucleotides in length). An oligonucleotide may be single-stranded (ss) or ds. An oligonucleotide may or may not have duplex regions. As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (dsiRNA), antisense oligonucleotide (ASO), short siRNA, or ss siRNA. Typically, a ds oligonucleotide is a RNAi oligonucleotide.

[0088] As used herein, “overhang” means a terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which

the one strand or region forms a duplex. An overhang may include one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a ds oligonucleotide. The overhang can be a 3' or 5' overhang on the antisense strand or sense strand of a ds oligonucleotides.

[0089] As used herein, “phosphate analog” means a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. A 5' phosphate analog can include a phosphatase-resistant linkage. Examples of phosphate analogs include, but are not limited to, 5' phosphonates, such as 5' methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). An oligonucleotide can have a phosphate analog at a 4'-carbon position of the sugar (referred to as a “4'-phosphate analog”) at a 5'-terminal nucleotide. An example of a 4'-phosphate analog is oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. *See, e.g.*, Intl. Patent Application Publication No. WO 2018/045317. Other modifications have been developed for the 5' end of oligonucleotides (*see, e.g.*, Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash *et al.* (2015) NUCLEIC ACIDS RES. 43:2993-3011).

[0090] As used herein, “APOC3-associated disease,” “APOC3-associated disorder” or “APOC3-associated condition” means conditions where increased APOC3 expression and/or the presence of, for example, a APOC3 polymorphism. Exemplary APOC3-associated conditions, diseases or disorders include, but are not limited to, AH, ACD, ALD, CCA, CHD, MetS, PSC, cirrhosis, hepatic fibrosis, hepatic inflammation, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual such as, for example, hyperlipidemia, diabetes and/or obesity.

[0091] As used herein, “reduced expression,” and with respect to a gene (*e.g.*, *APOC3*) means a decrease in the amount or level of RNA transcript (*e.g.*, *APOC3* mRNA) or protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a sample, or an individual, when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample, or individual). For example, the act of contacting a cell with an oligonucleotide herein (*e.g.*, an oligonucleotide having an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence including *APOC3* mRNA) may result in a decrease in the amount or level of mRNA, protein, and/or activity (*e.g.*, *via* degradation of *APOC3* mRNA by the RNAi pathway) when compared to a

cell that is not treated with the ds oligonucleotide. Similarly, and as used herein, “reducing expression” means an act that results in reduced expression of a gene (*e.g.*, *APOC3*). Specifically, and as used herein, “reduction of APOC3 expression” means a decrease in the amount or level of APOC3 mRNA, APOC3 protein, and/or APOC3 activity in a cell, a population of cells, a sample, or an individual when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, tissue, or individual).

[0092] As used herein, “region of complementarity” means a sequence of nucleotides of a nucleic acid (*e.g.*, a ds oligonucleotide) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cell, *etc.*). An oligonucleotide herein includes a targeting sequence having a region of complementarity to a mRNA target sequence.

[0093] As used herein, “ribonucleotide” means a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2' position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the nucleobase, sugar, or phosphate group.

[0094] As used herein, “RNAi oligonucleotide” refers to either (a) a ds oligonucleotide having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the *Argonaute 2* (Ago2) endonuclease in the cleavage of a target mRNA or (b) a ss oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA.

[0095] As used herein, “strand” refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (*e.g.*, phosphodiester linkages or phosphorothioate linkages). A strand can have two free ends (*e.g.*, a 5' end and a 3' end).

[0096] As used herein, “individual” means any mammal, including cats, dogs, mice, rats, and primates, especially humans. Moreover, “subject” or “patient” may be used interchangeably with “individual.”

[0097] As used herein, “synthetic” refers to a nucleic acid or other molecule that is artificially synthesized (*e.g.*, using a machine such as, for example, a solid-state nucleic acid synthesizer) or that is otherwise not derived from a natural source (*e.g.*, a cell or organism) that normally produces the nucleic acid or other molecule.

[0098] As used herein, “targeting ligand” means a molecule (*e.g.*, an amino sugar, carbohydrate, cholesterol, lipid, or polypeptide) that selectively binds to a cognate molecule (*e.g.*, a receptor) of a tissue or cell of interest and that is conjugatable to another substance for targeting another substance to the tissue or cell of interest. For example, a targeting ligand may be conjugated to an oligonucleotide herein for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. A targeting ligand can selectively bind to a cell surface receptor. Accordingly, a targeting ligand, when conjugated to an oligonucleotide, facilitates delivery of the oligonucleotide into a particular cell through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand, and receptor. Moreover, a targeting ligand can be conjugated to an oligonucleotide *via* a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell.

[0099] As used herein, “tetraloop” means a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a tetraloop can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C, or at least about 75°C in 10 mM NaHPO₄ to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. A tetraloop also may stabilize a bp in an adjacent stem duplex by stacking interactions. Additionally, interactions among the nucleotides in a tetraloop include, but are not limited to, non-Watson-Crick base pairing, stacking interactions, hydrogen bonding, and contact interactions (Cheong *et al.* (1990) NATURE 346:680-82; Heus & Pardi (1991) SCIENCE 253:191-94). Here, a tetraloop can include or can have about 3 to 6 nucleotides, and typically is about 4 to 5 nucleotides. A tetraloop therefore can have 3, 4, 5, or 6 nucleotides, which may or may not be modified (*e.g.*, which may or may not be conjugated to a targeting moiety), especially 4 nucleotides. Any nucleotide may be used in the tetraloop, and standard IUPAC-IUB symbols for such nucleotides may be used as described in Cornish-Bowden (1985) NUCLEIC ACIDS RES. 13:3021-30. For example, the letter “N” may be used to mean that any base may be in that position, the letter “R” may be used to show that A (adenine) or G (guanine) may be in that position, and “B” may be used to show that C (cytosine), G (guanine), or T (thymine) may be in that position. Examples of tetraloops include the UNCG family of tetraloops (*e.g.*, UUCG), the GNRA family of

tetraloops (*e.g.*, GAAA) and the CUUG tetraloop (Woese *et al.* (1990) PROC. NATL. ACAD. SCI. USA 87:8467-71; Antao *et al.* (1991) NUCLEIC ACIDS RES. 19:5901-05). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (*e.g.*, d(GTTA)), the d(GNRA) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (*e.g.*, d(TTCG)). *See, e.g.*, Nakano *et al.* (2002) BIOCHEM. 41:4281-92; and Shinji *et al.* (2000) NIPPON KAGAKKAI KOEN YOKOSHU 78:731. Here, the tetraloop can be within a nicked tetraloop structure.

[00100] As used herein, “treat” or “treating” means an act of providing care to an individual in need thereof, for example, by administering a therapeutic agent (*e.g.*, an oligonucleotide herein) to the individual for purposes of improving the health and/or well-being of the individual with respect to an existing condition (*e.g.*, a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. Treating also can involve reducing the frequency or severity of at least one sign, symptom or contributing factor of a condition (*e.g.*, disease, disorder) experienced by the individual.

[00101] As used herein, “iRNA,” “iRNA agent,” “RNAi,” “RNAi agent” and “RNA interference agent” means an agent that contains RNA and that mediates the targeted cleavage of an RNA-containing transcript *via* an RNA-induced silencing complex (RISC) pathway. RNAi directs sequence-specific degradation of mRNA *via* RNA interference. The RNAi modulates, inhibits, or reduces *APOC3* expression in a cell.

Compositions

[00102] According to some aspects, the disclosure provides oligonucleotides (*e.g.*, ds RNAi oligonucleotides) that reduce, modulate, or inhibit expression of *APOC3* in the liver. In some embodiments, the oligonucleotides provided herein are used to treat of diseases associated with *APOC3* expression. In some aspects, the disclosure provides methods of treatment of a disease associated with *APOC3* expression by reducing, modulating, or inhibiting *APOC3* expression in the liver (*e.g.*, in cells comprising the liver).

[00103] Oligonucleotide Inhibitors of APOC3 Expression

[00104] I. *APOC3* Target Sequences: The oligonucleotides herein (*e.g.*, RNAi oligonucleotides) are targeted to a target sequence comprising *APOC3* mRNA (*i.e.*, a *APOC3* target sequence). In some embodiments, the oligonucleotide or a portion, fragment, or strand thereof (*e.g.*, an antisense strand or a guide strand of a ds RNAi oligonucleotide) binds or anneals to an *APOC3* target sequence, thereby inhibiting *APOC3* expression. In some

embodiments, the oligonucleotide is targeted to a APOC3 target sequence for inhibiting *APOC3* expression *in vivo*. In some embodiments, the amount or extent of *APOC3* expression inhibition by an oligonucleotide targeted to an APOC3 target sequence correlates with the potency of the oligonucleotide. In some embodiments, the amount or extent of inhibition of *APOC3* expression by an oligonucleotide targeted to an APOC3 target sequence correlates with the amount or extent of therapeutic benefit in an individual having or suspected of having a disease, disorder, or condition associated with *APOC3* expression treated with the oligonucleotide.

[00105] Through examining and analyzing the nucleotide sequence of APOC3 mRNAs, including mRNAs of multiple different species (*e.g.*, human and cynomolgus monkey; *see, e.g.*, Example 1) and because of *in vitro* and *in vivo* testing (*see, e.g.*, Examples 2-3), it is shown herein that certain nucleotide sequences of APOC3 mRNA are more amenable than others to oligonucleotide-based inhibition of *APOC3* expression and are thus useful as target sequences for the oligonucleotides herein. In some embodiments, a sense strand of an oligonucleotide (*e.g.*, a ds RNAi oligonucleotide) described herein (*e.g.*, Table 2 or 3) comprises an APOC3 target sequence. In some embodiments, a portion or region of the sense strand of an oligonucleotide described herein (*e.g.*, Table 2 or 3) comprises a APOC3 target sequence. In some embodiments, the APOC3 target sequence comprises, or consists of, a sequence of any one of SEQ ID NOs:334 to 341.

[00106] II. APOC3 mRNA Targeting Sequences: In some embodiments, the oligonucleotides herein have regions of complementarity to APOC3 mRNA (*e.g.*, within a target sequence of APOC3 mRNA) for targeting APOC3 mRNA in cells and inhibiting *APOC3* expression. In some embodiments, the oligonucleotides herein comprise an APOC3 targeting sequence (*e.g.*, an antisense strand or a guide strand of a ds oligonucleotide) having a region of complementarity that binds or anneals to an APOC3 mRNA target sequence by complementary (Watson-Crick) base pairing. The targeting sequence or region of complementarity is of a suitable length and base content to enable binding or annealing of the oligonucleotide (or a strand thereof) to APOC3 mRNA for inhibiting its expression. In some embodiments, the targeting sequence or region of complementarity is at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29, or at least about 30 nucleotides in length. Alternatively, the targeting sequence or region of

complementarity is about 12 to about 30 (*e.g.*, 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. Alternatively, the targeting sequence or region of complementarity is about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 18 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 19 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 20 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 21 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 22 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 23 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 24 nucleotides in length.

[00107] In some embodiments, the oligonucleotides herein comprise a targeting sequence or a region of complementarity (*e.g.*, an antisense strand or a guide strand of a ds oligonucleotide) that is fully complementary to an APOC3 target sequence. In some embodiments, the targeting sequence or region of complementarity is partially complementary to an APOC3 target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs:334 to 341. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs:334 to 341.

[00108] Alternatively, in some embodiments, the oligonucleotides herein comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an APOC3 mRNA, where the contiguous sequence of nucleotides is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 28, 12 to 26, 12 to 24, 12 to 20, 12 to 18, 12 to 16, 14 to 22, 16 to 20, 18 to 20, or 18 to 19 nucleotides in length). In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an APOC3 mRNA, where the contiguous sequence of nucleotides is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an APOC3 mRNA, where the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotides comprise a

targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising an APOC3 mRNA, where the contiguous sequence of nucleotides is 20 nucleotides in length. In other embodiments, the oligonucleotides comprise a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs:334 to 341, optionally where the contiguous sequence of nucleotides is 19 nucleotides in length.

[00109] Regarding the targeting sequence or region of complementarity of the oligonucleotides herein, it is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs:334 to 341 and spans the entire length of an antisense strand. In some embodiments, the region of complementarity of the oligonucleotides is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs:334 to 341 and spans a portion of the entire length of an antisense strand. In some additional embodiments, the oligonucleotides include a region of complementarity (*e.g.*, on an antisense strand of a ds oligonucleotide) that is at least partially (*e.g.*, fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20, 1-19, 1-18, *etc.* of a sequence as set forth in any one of SEQ ID NOs:334 to 341.

[00110] Alternatively, the oligonucleotides herein comprise a targeting sequence or region of complementarity having one or more base pair (bp) mismatches with the corresponding APOC3 target sequence. In some embodiments, the targeting sequence or region of complementarity is up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding APOC3 target sequence, provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the APOC3 mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to reduce or inhibit *APOC3* expression is maintained. Stated differently, the targeting sequence or region of complementarity is no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding APOC3 target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to an APOC3 mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotides to reduce or inhibit *APOC3* expression is maintained. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 1 mismatch with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 2 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or

a region of complementarity having 3 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 4 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 5 mismatches with the corresponding target sequence. In other embodiments, the oligonucleotides comprise a targeting sequence or a region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, where at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or where the mismatches are interspersed in any position throughout the targeting sequence or region of complementarity. In other embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, where at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or where at least one or more non-mismatched bp is located between the mismatches, or a combination thereof.

[00111] III. Types of Oligonucleotides: A variety of oligonucleotide types and/or structures are useful for targeting *APOC3* mRNA including, but not limited to, RNAi oligonucleotides, antisense oligonucleotides, miRNAs, *etc.* Any of the oligonucleotide types described herein or elsewhere are contemplated for use as a framework to incorporate a targeting sequence herein for the purposes of inhibiting *APOC3* expression. In some embodiments, the oligonucleotides herein inhibit *APOC3* expression by engaging with RNAi pathways upstream or downstream of Dicer involvement. For example, RNAi oligonucleotides have been developed with each strand having sizes of about 19-25 nucleotides with at least one 3' overhang of 1 to 5 nucleotides (*see, e.g.*, US Patent No. 8,372,968). Longer oligonucleotides also have been developed that are processed by Dicer to generate active RNAi products (*see, e.g.*, US Patent No. 8,883,996). Further work produced extended ds oligonucleotides where at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically stabilizing tetraloop structure (*see, e.g.*, US Patent Nos. 8,513,207 and 8,927,705, as well as Intl. Patent Application Publication No. WO 2010/033225). Such structures include ss extensions (on one or both sides of the molecule) as well as ds extensions.

[00112] The oligonucleotides herein engage with the RNAi pathway downstream of the involvement of Dicer (*e.g.*, Dicer cleavage). In some embodiments, the oligonucleotides have

an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3' end of the sense strand. In some embodiments, the oligonucleotides (*e.g.*, siRNA) include a 21-nucleotide antisense strand that is antisense to a target mRNA (*e.g.*, APOC3 mRNA) and a complementary sense strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3' ends. Longer oligonucleotide designs also are contemplated, including oligonucleotides having an antisense strand of 23 nucleotides and a sense strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3' end of sense strand/5' end of antisense strand) and a two nucleotide 3'-antisense strand overhang on the left side of the molecule (5' end of the sense strand/3' end of the antisense strand). In such molecules, there is a 21 bp duplex region. *See, e.g.*, US Patent Nos. 9,012,138; 9,012,621 and 9,193,753.

[00113] The oligonucleotides herein comprise sense and antisense strands that are both in the range of about 17 to about 26 (*e.g.*, 17 to 26, 20 to 25, or 21-23) nucleotides in length. In some embodiments, the oligonucleotides comprise a sense and antisense strand that are both in the range of about 19 to about 22 nucleotides in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, the oligonucleotides comprise sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, for oligonucleotides having sense and antisense strands that are both in the range of about 21 to about 23 nucleotides in length, a 3'-overhang on the sense, antisense or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotides comprise an antisense strand of 22 nucleotides and a sense strand of 20 nucleotides, where there is a blunt end on the right side of the molecule (3' end of sense strand/5' end of antisense strand) and a 2 nucleotide 3' antisense strand overhang on the left side of the molecule (5' end of the sense strand/3' end of the antisense strand). In such molecules, there is a 20-bp duplex region.

[00114] Other oligonucleotide designs for use herein include: 16-mer siRNAs (*see, e.g.*, "NUCLEIC ACIDS IN CHEMISTRY & BIOLOGY," Blackburn (ed.), Royal Society of Chemistry, 2006), shRNAs (*e.g.*, having 19 bp or shorter stems; *see, e.g.*, Moore *et al.* (2010) METHODS MOL. BIOL. 629:141-58), blunt siRNAs (*e.g.*, of 19 bps in length; *see, e.g.*, Kraynack & Baker (2006) RNA 12:163-76), asymmetrical siRNAs (aiRNA; *see, e.g.*, Sun *et al.* (2008) NAT. BIOTECHNOL. 26:1379-82), asymmetric shorter-duplex siRNA (*see, e.g.*, Chang *et al.* (2009) MOL. THER. 17:725-32), fork siRNAs (*see, e.g.*, Hohjoh (2004) FEBS LETT. 557:193-98), ss siRNAs (*see, e.g.*, Elsner (2012) NAT. BIOTECHNOL. 30:1063), dumbbell-shaped circular siRNAs (*see, e.g.*, Abe *et al.* (2007) J. AM. CHEM. SOC. 129:15108-09), and small internally

segmented interfering RNA (sisiRNA; *see, e.g.*, Bramsen *et al.* (2007) NUCLEIC ACIDS RES. 35:5886-97). Further non-limiting examples of oligonucleotide structures that may be used herein to reduce or inhibit *APOC3* expression are miRNA, shRNA, and short siRNA (*see, e.g.*, Hamilton *et al.* (2002) EMBO J. 21:4671-79; *see also*, US Patent No. 7,659,389).

[00115] Alternatively, the oligonucleotides herein are ss. Such structures include, but are not limited to, ss RNAi molecules. Recent efforts have demonstrated the activity of ss RNAi molecules (*see, e.g.*, Matsui *et al.* (2016) MOL. THER. 24:946-55). In some embodiments, the oligonucleotides are ASOs. An ASO is a ss oligonucleotide that has a nucleobase sequence which, when written or depicted in the 5' to 3' direction, includes a reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (*e.g.*, as a gapmer) to induce RNaseH-mediated cleavage of its target RNA in cells or (*e.g.*, as a mixmer) so as to inhibit translation of the target mRNA in cells. ASOs for use herein are modified in any suitable manner known in the art including, for example, as shown in US Patent No. 9,567,587 (including, for example, length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, ASOs have been used for decades to reduce expression of specific target genes (*see, e.g.*, Bennett *et al.* (2017) ANNU. REV. PHARMACOL. 57:81-105).

[00116] IV. ds RNAi Oligonucleotides: ds oligonucleotides for targeting *APOC3* mRNA and inhibiting *APOC3* expression (*e.g.*, *via* the RNAi pathway) comprising a sense strand (*i.e.*, a passenger strand) and an antisense strand (*i.e.*, a guide strand). In some embodiments, the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked.

[00117] In some embodiments, the sense strand comprises a first region (R1) and a second region (R2), where R2 comprises a first subregion (S1), a triL or a L, and a second subregion (S2), where triL or L is located between S1 and S2, and where S1 and S2 form a second duplex (D2). D2 has various lengths. In some embodiments, D2 is about 1 to about 6 bp in length. In other embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5 or 4-5 bp in length. In other embodiments, D2 is 1, 2, 3, 4, 5 or 6 bp in length. In certain embodiments, D2 is 6 bp in length.

[00118] In some embodiments, R1 of the sense strand and the antisense strand forms a first duplex (D1). In some embodiments, D1 is at least about 15 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21) nucleotides in length. In other embodiments, D1 is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30 or 21 to 30 nucleotides in length). In other embodiments, D1 is at least

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

[00119] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *APOC3* expression that include a sense strand having (comprising or consisting of) a sequence as set forth in Table 2 (*e.g.*, any one of the odd numbers of SEQ ID NOs:9 to 170), especially SEQ ID NOs:37, 43, 45, 87, 89, 99, 101, and 105.

[00120] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *APOC3* expression that include an antisense strand having (comprising or consisting of) a sequence as set forth in Table 2 (*e.g.*, any one of the even numbers of SEQ ID NOs:9 to 170), especially SEQ ID NOs:38, 44, 46, 88, 90, 100, 102, and 106.

[00121] In certain other embodiments, the RNAi oligonucleotide includes a sense strand having (comprising or consisting of) a nucleotide sequence of any one of SEQ ID NOs:37, 43, 45, 87, 89, 99, 101, and 105, and an antisense strand having (comprising, or consisting of) a nucleotide sequence of any one of SEQ ID NOs:38, 44, 46, 88, 90, 100, 102, and 106.

[00122] In certain additional embodiments, the RNAi oligonucleotide includes a sense strand having (comprising or consisting of) a nucleotide sequence of any one of SEQ ID NOs:37, 89 and 101, and an antisense strand having (comprising, or consisting of) a nucleotide sequence of any one of SEQ ID NOs:38, 90 and 102.

[00123] In certain embodiments, the sense strand, and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

- (a) SEQ ID NOs:37 and 38,
- (b) SEQ ID NOs:43 and 44,
- (c) SEQ ID NOs:45 and 46,
- (d) SEQ ID NOs:87 and 88,
- (e) SEQ ID NOs:89 and 90,
- (f) SEQ ID NOs:99 and 100,
- (g) SEQ ID NOs:101 and 102, and
- (h) SEQ ID NOs:105 and 106.

[00124] In some embodiments, the RNAi oligonucleotide includes a sense strand having (comprising or consisting of) a nucleotide sequence as set forth in Table 3 (*e.g.*, any one of the odd numbers of SEQ ID NOs:171 to 332), especially SEQ ID NOs:199, 205, 207, 249, 251, 261, 263, and 267.

[00125] In certain embodiments, the RNAi oligonucleotide includes an antisense strand having (comprising or consisting of) a nucleotide sequence as set forth in Table 3 (*e.g.*, any one of the even numbers of SEQ ID NOs:171 to 332), especially 200, 206, 208, 250, 252, 262, 264, and 268.

[00126] In certain other embodiments, the RNAi oligonucleotide includes a sense strand having (comprising or consisting of) a nucleotide sequence of any one of SEQ ID NOs:199, 205, 207, 249, 251, 261, 263 and 267, and an antisense strand having (comprising, or consisting of) a nucleotide sequence of any one of SEQ ID NOs: 200, 206, 208, 250, 252, 262, 264 and 268.

[00127] In certain additional embodiments, the RNAi oligonucleotide includes a sense strand having (comprising or consisting of) a nucleotide sequence of any one of SEQ ID NOs:199, 251 and 263, and an antisense strand having (comprising, or consisting of) a nucleotide sequence of any one of SEQ ID NOs:200, 252 and 264.

[00128] In certain embodiments, the sense strand, and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

- (a) SEQ ID NOs:199 and 200,
- (b) SEQ ID NOs:205 and 206,
- (c) SEQ ID NOs:207 and 208,
- (d) SEQ ID NOs:249 and 250,
- (e) SEQ ID NOs:251 and 252,
- (f) SEQ ID NOs:261 and 262,
- (g) SEQ ID NOs:263 and 264, and
- (h) SEQ ID NOs:267 and 268.

[00129] One of skill in the art appreciates that in some embodiments, the sequences presented in the Sequence Listing is referred to in describing the structure of an oligonucleotide (*e.g.*, a ds oligonucleotide) or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid has one or more alternative nucleotides (*e.g.*, an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other

modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[00130] In some embodiments, a ds oligonucleotide herein includes a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In other embodiments, the sense strand of the ds oligonucleotide is longer than 25 nucleotides (*e.g.*, 26, 27, 28, 29, or 30 nucleotides). In other embodiments, the sense strand of the ds oligonucleotide is longer than 27 nucleotides (*e.g.*, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides).

[00131] In some embodiments, the ds oligonucleotides herein have one 5' end that is thermodynamically less stable when compared to the other 5' end. In some embodiments, the ds oligonucleotide is asymmetric and includes a blunt end at the 3' end of a sense strand and a 3'-overhang at the 3' end of an antisense strand. In some embodiments, the 3'-overhang on the antisense strand is about 1 to about 8 nucleotides in length (*e.g.*, 1, 2, 3, 4, 5, 6, 7, or 8 nucleotides in length). Typically, a ds oligonucleotide for RNAi has a two-nucleotide overhang on the 3' end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3'-overhang having a length of between about 1 to about 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5, or 6 nucleotides. However, in other embodiments, the overhang is a 5'-overhang comprising a length of between about 1 to about 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5, or 6 nucleotides.

[00132] In some embodiments, two terminal nucleotides on the 3' end of an antisense strand are modified. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand are complementary with the target mRNA (*e.g.*, APOC3 mRNA). In other embodiments, the two terminal nucleotides on the 3' end of the antisense strand are not complementary with the target mRNA. In some embodiments, two terminal nucleotides on each 3' end of an oligonucleotide in the nicked tetraloop structure are GG. Typically, one or both of the two terminal GG nucleotides on each 3' end of a ds oligonucleotide is not complementary with the target mRNA.

[00133] In some embodiments, there is one or more (*e.g.*, 1, 2, 3, 4, or 5) mismatch(s) between the sense and antisense strand. If there is more than one mismatch between the sense and antisense strand, they may be positioned consecutively (*e.g.*, 2, 3, or more in a row), or interspersed throughout the region of complementarity. In some embodiments, the 3' end of the

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

[00134] A. Sense Strands: The oligonucleotides (*e.g.*, a ds oligonucleotide) herein for targeting an APOC3 mRNA and inhibiting *APOC3* expression include a sense strand sequence including a sequence as set forth in the sense strands of Table 2 or Table 3. In some embodiments, the oligonucleotides include a sense strand that having at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in in any one of SEQ ID NOs:37, 43, 45, 87, 89, 99, 101 and 105, or a sense strand having a nucleotide sequence of any one of SEQ ID NOs:199, 205, 207, 249, 251, 261, 263 and 267.

[00135] Further, the oligonucleotides (*e.g.*, a ds oligonucleotide) herein include a sense strand (or passenger strand) of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 36, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17, or up to 12 nucleotides in length). In some embodiments, the oligonucleotides can have a sense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 36, or at least 38 nucleotides in length). Alternatively, the oligonucleotides can have a sense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In certain embodiments, the oligonucleotides can have a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length.

[00136] In some embodiments, the sense strand comprises a stem-loop structure at its 3' end. In other embodiments, the sense strand comprises a stem-loop structure at its 5' end. In additional embodiments, the stem is a duplex of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 bp in length. In some embodiments, the stem-loop provides the oligonucleotides protection against degradation (*e.g.*, enzymatic degradation) and facilitates or improves targeting and/or delivery to a target cell, tissue, or organ (*e.g.*, the liver), or both. For example, the loop of the stem-loop provides nucleotides having one or more modifications that facilitate, improve, or increase targeting to a target mRNA (*e.g.*, an APOC3 mRNA), inhibiting of target gene expression (*e.g.*, *APOC3* expression), and/or delivering to a target cell, tissue, or organ (*e.g.*, the liver), or both. In some embodiments, the stem-loop itself or modification(s) to the stem-

loop do not substantially affect the inherent gene expression inhibition activity of the oligonucleotide, but facilitates, improves, or increases stability (*e.g.*, provides protection against degradation) and/or delivery of the oligonucleotide to a target cell, tissue, or organ (*e.g.*, the liver). In certain embodiments, the oligonucleotides comprise a sense strand including (*e.g.*, at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a ss loop between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length). In certain embodiments, the loop (L) is 4 nucleotides in length. FIGS. 1A-1C depict non-limiting examples of such an oligonucleotide. In some embodiments the loop (L) of the stem-loop having the structure S1-L-S2 as described above is a tetraloop (*e.g.*, within a nicked tetraloop structure). In some embodiments, the tetraloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, delivery ligands and combinations thereof.

[00137] B. Antisense Strands: The oligonucleotides (*e.g.*, a ds oligonucleotide) herein for targeting an APOC3 mRNA and inhibiting *APOC3* expression include an antisense strand including a sequence as set forth in the antisense strands of Table 2 or Table 3. In some embodiments, the oligonucleotides include an antisense strand having at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs:38, 44, 46, 88, 90, 100, 102 and 106, or an antisense strand having a nucleotide sequence of any one of SEQ ID NOs:200, 206, 208, 250, 252, 262, 264 and 268.

[00138] Further, the oligonucleotides (*e.g.*, a ds oligonucleotide) herein can include an antisense strand of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17, or up to 12 nucleotides in length). In some embodiments, the oligonucleotides can have an antisense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 22, at least 25, at least 27, at least 30, at least 35, or at least 38 nucleotides in length). Alternatively, the oligonucleotides can have an antisense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 22, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In certain embodiments, the oligonucleotide can have an antisense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length.

[00139] As noted above, the antisense strand of the oligonucleotides herein may be referred to as the "guide strand." For example, the antisense strand that engages with RISC and that

binds to an *Argonaute* protein such as Ago2, or that engages with or that binds to one or more similar factors, and directs silencing of a target gene, the antisense strand is referred to as a guide strand (or “passenger strand”).

[00140] V. Oligonucleotide Modifications:

[00141] A. Sugar Modifications: A modified sugar (also referred to herein as a sugar analog) includes a modified deoxyribose or ribose moiety in which, for example, one or more modifications occur at the 2', 3', 4', and/or 5' carbon position of the sugar. A modified sugar also includes non-natural, alternative, carbon structures such as those present in locked nucleic acids (“LNA”; *see, e.g.,* Koshkin *et al.* (1998) TETRAHEDRON 54:3607-30), unlocked nucleic acids (“UNA”; *see, e.g.,* Snead *et al.* (2013) MOL. THER-NUC. ACIDS 2:e103) and bridged nucleic acids (“BNA”; *see, e.g.,* Imanishi & Obika (2002) CHEM. COMMUN. 16:1653-59).

[00142] In some embodiments, the nucleotide modification in the sugar is a 2'-modification such as, for example, 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-F, 2'-aminoethyl (EA), 2'-OMe, 2'-MOE, 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), or 2'-FANA. In certain embodiments, the modification is 2'-F, 2'-OMe, or 2'-MOE. In other embodiments, the modification in the sugar is a modification of the sugar ring, which includes modification of one or more carbons of the sugar ring. For example, the modification in the sugar is a 2'-oxygen of the sugar linked to a 1'-carbon or 4'-carbon of the sugar, or a 2'-oxygen linked to the 1'-carbon or 4'-carbon *via* an ethylene or methylene bridge. In other embodiments, the modification is an acyclic sugar that lacks a 2'-carbon to 3'-carbon bond. In other embodiments, the modification is a thiol group such as, for example, in the 4' position of the sugar.

[00143] The oligonucleotides herein include at least 1 modified nucleotide (*e.g.,* at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand comprises at least 1 modified nucleotide (*e.g.,* at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand comprises at least 1 modified nucleotide (*e.g.,* at least 1, at least 5, at least 10, at least 15, at least 20, or more).

[00144] In certain embodiments, all nucleotides of the sense strand except the tetraloop are modified. Likewise, all nucleotides of the antisense strand are modified. In some embodiments, all the ds nucleotides of the oligonucleotides herein (*i.e.,* paired nucleotides of the sense strand and the antisense strand) are modified. As above, and in some embodiments, the modified nucleotide is a 2'-modification (*e.g.,* a 2'-F, 2'-OMe, 2'-MOE, and/or 2'-FANA. In certain

embodiments, the modified nucleotide is a 2'-modification such as, for example, a 2'-F or a 2'-OMe.

[00145] Moreover, the oligonucleotides herein have different modification patterns. In some embodiments, the modified oligonucleotides comprise an antisense strand having a modification pattern as set forth in Table 3 and comprise a sense strand sequence having a modification pattern as set forth in Table 3 (as well as FIGS. 1A-1C). In some embodiments, one or more of positions 8, 9, 10, or 11 of the sense strand are modified with a 2'-F. In other embodiments, the sugar moiety at each nucleotide at positions 1 to 7, 12 to 27 and 31 to 36 in the sense strand is modified with a 2'-OMe. In certain embodiments, positions 8 to 11 of the sense strand are modified with a 2'-F and positions 1 to 7, 12 to 27 and 31 to 36 are modified with a 2'-OMe.

[00146] In certain additional embodiments, a sense strand comprising a 2'-F modified nucleotide at positions 8-11, a 2'-OMe modified nucleotide at positions 1 to 7, 12 to 27 and 31 to 36, a GalNAc-conjugated nucleotide at position 28, 29 and 30, and a phosphorothioate linkage between positions 1 and 2.

[00147] In some embodiments, the antisense strand comprises one or more nucleotides at positions 2-5, 7, 10 and 14 modified with 2'-F, and one or more nucleotides at positions 1, 6, 8 to 9, 11 to 13 and 15 to 22 modified with a 2'-OMe. Certain embodiments disclose an oligonucleotide with an antisense strand comprising a 2'-F-modified nucleotide at positions 2 to 5, 7, 10 and 14, and a 2'-OMe-modified nucleotide at positions 1, 6, 8 to 9, 11 to 13 and 15 to 22.

[00148] In certain embodiments the antisense strand comprises a 2'-F modified nucleotide at positions 2 to 5, 7, 10 and 14, a 2'-OMe at positions 1, 6, 8 to 9, 11 to 13 and 15 to 22, a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, positions 3 and 4, positions 20 and 21, and positions 21 and 22

[00149] B. 5'-Terminal Phosphates: 5'-terminal phosphate groups can be used to enhance the interaction of the oligonucleotides herein with Ago2. However, oligonucleotides having a 5'-phosphate group may be susceptible to degradation *via* phosphatases or other enzymes, which can limit their bioavailability *in vivo*. In some embodiments, the oligonucleotides herein (*e.g.*, a ds oligonucleotide) comprise analogs of 5' phosphates that are resistant to such degradation. Examples of such phosphate analogs include, but are not limited to, oxymethylphosphonate, vinylphosphonate, malonyl phosphonate, or a combination thereof. In certain embodiments the

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

[00150] Alternatively, or additionally, the oligonucleotides herein have a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog"). *See, e.g.*, Intl. Patent Application Publication No. WO 2018/045317. In some embodiments, the oligonucleotides herein include a 4'-phosphate analog at a 5'-terminal nucleotide. In some embodiments, the phosphate analog is an oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. In other embodiments, the 4'-phosphate analog is a thiomethylphosphonate or an aminomethylphosphonate, in which the sulfur atom of the thiomethyl group or the nitrogen atom of the amino methyl group is bound to the 4'-carbon of the sugar moiety or analog thereof. In certain embodiments, the 4'-phosphate analog is an oxymethylphosphonate, which is represented by the formula $-O-CH_2-PO(OH)_2$ or $-O-CH_2-PO(OR)_2$, in which R is independently selected from H, CH₃, an alkyl group, CH₂CH₂CN, CH₂OCOC(CH₃)₃, CH₂OCH₂CH₂Si(CH₃)₃, or a protecting group. In certain embodiments, the alkyl group is CH₂CH₃. In certain other embodiments, R is independently selected from H, CH₃, or CH₂CH₃.

[00151] C. Modified Internucleotide Linkages: In addition to the above modifications, the oligonucleotides herein (*e.g.*, a ds oligonucleotide) comprise a modified internucleotide linkage. In some embodiments, phosphate modifications or substitutions result in oligonucleotides that comprise at least about 1 (*e.g.*, at least 1, at least 2, at least 3, or at least 5) modified internucleotide linkages. In some embodiments, the oligonucleotides herein (*e.g.*, a ds oligonucleotide) comprise about 1 to about 10 (*e.g.*, 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3, or 1 to 2) modified internucleotide linkages. In other embodiments, the oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 modified internucleotide linkages.

[00152] Examples of modified internucleotide linkages include, but are not limited, to, a phosphorodithioate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage, or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage.

[00153] In some embodiments, the oligonucleotides herein include a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense

strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In other embodiments, the oligonucleotides comprise a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

[00154] In certain embodiments, an oligonucleotide herein includes:

a sense strand having a 2'-F modified nucleotide at positions 8 to 11, a 2'-OMe modified nucleotide at positions 1 to 7, 12 to 27 and 31 to 36, a GalNAc-conjugated nucleotide at position 28, 29 and 30, and a phosphorothioate linkage between positions 1 and 2;

an antisense strand having a 2'-F modified nucleotide at positions 2 to 5, 7, 10 and 14, a 2'-OMe at positions 1, 6, 8 to 9, 11 to 13 and 15 to 22, a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, positions 3 and 4, positions 20 and 21, and positions 21 and 22, and a 5'-terminal nucleotide at position 1 comprising a 4'-phosphate analog, optionally wherein the 5'-terminal nucleotide comprises 4-O-monomethylphosphonate-2'-O-methyl uridine [MePhosphonate-4O-mU]; where positions 1 to 20 of the antisense strand form a duplex region with positions 1 to 20 of the sense strand, where positions 21 to 36 of the sense strand form a stem-loop, where positions 27 to 30 form the loop of the stem-loop, optionally where positions 27 to 30 comprise a tetraloop, where positions 21 and 22 of the antisense strand comprise an overhang, and where the sense strand and antisense strands include nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs:199 and 200,
- (b) SEQ ID NOs:205 and 206,
- (c) SEQ ID NOs:207 and 208,
- (d) SEQ ID NOs:249 and 250,
- (e) SEQ ID NOs:251 and 252,
- (f) SEQ ID NOs:261 and 262,
- (g) SEQ ID NOs:263 and 264, and
- (h) SEQ ID NOs:267 and 268.

[00155] D. Base Modifications: In addition to the above modifications, the oligonucleotides herein (*e.g.*, a ds oligonucleotide) also comprise one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1' position of a nucleotide sugar moiety. In some embodiments, the modified nucleobase is a nitrogenous base. In other embodiments, the modified nucleobase does not contain nitrogen

atom. *See, e.g.*, US Patent Application Publication No. 2008/0274462. In certain other embodiments, the modified nucleotide is a universal base. However, in certain embodiments, the modified nucleotide does not contain a nucleobase (abasic).

[00156] With regard to universal bases, they comprise a heterocyclic moiety located at the 1' position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a nucleotide sugar moiety substitution, that, when present in a duplex, is positioned opposite more than one type of base without substantially altering structure of the duplex. Moreover, and compared to a reference ss nucleic acid (*e.g.*, oligonucleotide) that is fully complementary to a target nucleic acid, a ss nucleic acid having a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. However, when compared to a reference ss nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the ss nucleic acid having the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid having the mismatched base.

[00157] Exemplary universal-binding nucleotides include, but are not limited to, inosine, 1- β -D-ribofuranosyl-5-nitroindole and/or 1- β -D-ribofuranosyl-3-nitropyrrole (*see, e.g.*, US Patent Application Publication No. 2007/0254362; Van Aerschot *et al.* (1995) NUCLEIC ACIDS RES. 23:4363-70; Loakes *et al.* (1995) NUCLEIC ACIDS RES. 23:2361-66; and Loakes & Brown (1994) NUCLEIC ACIDS RES. 22:4039-403).

[00158] E. Reversible Modifications: While certain modifications can be made to protect the oligonucleotides herein (*e.g.*, a ds oligonucleotide) from the *in vivo* environment before reaching target cells, they also can be made to reduce the potency or activity of the oligonucleotides once they reach the cytosol of the target cell. Reversible modifications therefore can be made such that the oligonucleotides retain desirable properties outside of the cell, which are then removed upon entering the cytosolic environment of the cell. Reversible modification can be removed, for example, by the action of an intracellular enzyme or by the chemical conditions inside of a cell (*e.g.*, through reduction by intracellular glutathione).

[00159] In some embodiments, a reversibly modified nucleotide comprises a glutathione-sensitive moiety. Typically, oligonucleotides are chemically modified with cyclic disulfide moieties to mask the negative charge created by the internucleotide diphosphate linkages and to improve cellular uptake and nuclease resistance. *See*, US Patent Application Publication No. 2011/0294869, Intl. Patent Application Publication Nos. WO 2014/088920 and WO 2015/188197, and Meade *et al.* (2014) NAT. BIOTECHNOL. 32:1256-63. This reversible

modification of the internucleotide diphosphate linkages is designed to be cleaved intracellularly by the reducing environment of the cytosol (*e.g.*, glutathione). Earlier examples include neutralizing phosphotriester modifications that are reported to be cleavable inside cells (*see, e.g.*, Dellinger *et al.* (2003) J. AM. CHEM. SOC. 125:940-50).

[00160] Some reversible modifications protect the oligonucleotides during *in vivo* administration (*e.g.*, transit through the blood and/or lysosomal/endosomal compartments of a cell) where the oligonucleotides will be exposed to nucleases and other harsh environmental conditions (*e.g.*, pH). When released into the cytosol of a cell where the levels of glutathione are higher compared to extracellular space, the modification is reversed, and the result is cleaved oligonucleotides. Using reversible, glutathione-sensitive moieties, it is possible to introduce sterically larger chemical groups into the oligonucleotides when compared to the options available using irreversible chemical modifications. This is because these larger chemical groups will be removed in the cytosol and, therefore, should not interfere with the biological activity of the oligonucleotides inside the cytosol of a cell. As a result, these larger chemical groups can be engineered to confer various advantages to the oligonucleotides, such as nuclease resistance, lipophilicity, charge, thermal stability, specificity, and reduced immunogenicity. In some embodiments, the structure of the glutathione-sensitive moiety can be engineered to modify the kinetics of its release.

[00161] In some embodiments, the glutathione-sensitive moiety is attached to the sugar of the nucleotide. In certain embodiments, the glutathione-sensitive moiety is attached to the 2'-carbon of the sugar of a modified nucleotide. Additionally, or alternatively, the glutathione-sensitive moiety is attached to the 5'-carbon of a sugar, particularly when the modified nucleotide is the 5'-terminal nucleotide of the oligonucleotides. Additionally, or alternatively, the glutathione-sensitive moiety is attached to the 3'-carbon of sugar, particularly when the modified nucleotide is the 3'-terminal nucleotide of the oligonucleotides. In some embodiments, the glutathione-sensitive moiety includes a sulfonyl group (*see, e.g.*, Intl. Patent Application Publication No. WO 2018/039364).

[00162] VI. Targeting Ligands: It is desirable to target the oligonucleotides herein (*e.g.*, a ds oligonucleotide) to one or more cells or one or more organs. Such a strategy can help to avoid undesirable effects in other organs or to avoid undue loss of the oligonucleotides to cells, tissue, or organs that would not benefit therefrom. Accordingly, the oligonucleotides can be modified to facilitate targeting and/or delivering to a tissue, cell, or organ (*e.g.*, to facilitate delivering the oligonucleotides to the liver). In some embodiments, the oligonucleotides are modified to

facilitate delivery of the oligonucleotide to the hepatocytes of the liver. In some embodiments, the oligonucleotides comprise at least one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6, or more nucleotides) conjugated to one or more targeting ligand(s).

[00163] Exemplary targeting ligands include, but are not limited to, a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein, or part of a protein (*e.g.*, an antibody or antibody fragment), or lipid. In some embodiments, the targeting ligand is an aptamer. For example, the targeting ligand is an Arg-Gly-Asp (RGD) peptide for targeting tumor vasculature or glioma cells, Cys-Arg-Glu-Lys-Ala (CREKA) peptide for targeting tumor vasculature or stoma, transferrin, lactoferrin, or an aptamer for targeting transferrin receptors expressed on central nervous system (CNS) vasculature, or an anti-epidermal growth factor receptor (EGFR) antibody for targeting EGFR on glioma cells. In certain embodiments, the targeting ligand is one or more GalNAc moieties.

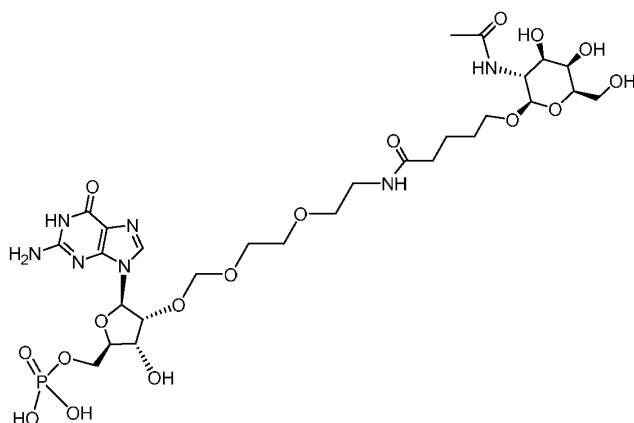
[00164] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5, or 6) nucleotides of the oligonucleotides each can be conjugated to a separate targeting ligand. In some embodiments, 2 to 4 nucleotides of the oligonucleotides each are conjugated to a separate targeting ligand. In other embodiments, targeting ligands can be conjugated to 2 to 4 nucleotides at either ends of the sense strand or antisense strand (*e.g.*, targeting ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense strand or antisense strand) such that the targeting ligands resemble bristles of a toothbrush, and the oligonucleotides resemble a toothbrush. For example, the oligonucleotides comprise a stem-loop at either the 5' or 3' end of the sense strand and 1, 2, 3, or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand. In some embodiments, the oligonucleotides comprise a stem-loop at the 3' end of the sense strand, where the loop of the stem-loop includes a triL or a L, and where the 3 or 4 nucleotides of the triL or L, respectfully, are individually conjugated to a targeting ligand.

[00165] GalNAc is a high affinity ligand for the ASGPR, which is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to the oligonucleotides herein are used to target them to the ASGPR expressed on cells. In some embodiments, the oligonucleotides are conjugated to at least one or more GalNAc moieties, where the GalNAc moieties target the oligonucleotides to an ASGPR expressed on human liver cells (*e.g.*, human hepatocytes).

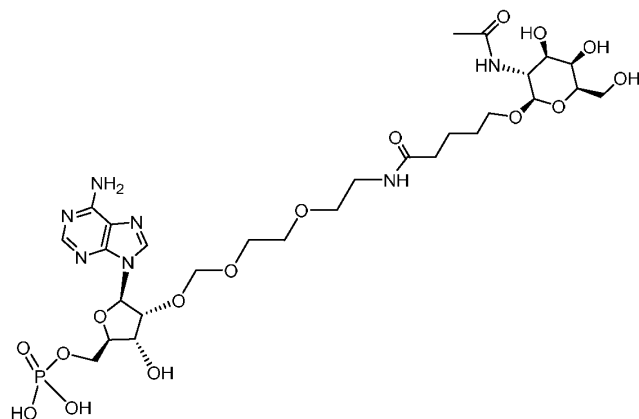
[00166] The oligonucleotides are conjugated directly or indirectly to a monovalent GalNAc. In some embodiments, the oligonucleotides are conjugated directly or indirectly to more than 1 monovalent GalNAc (*i.e.*, is conjugated to 2, 3, or 4 monovalent GalNAc moieties, and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, the oligonucleotides are conjugated to one or more bivalent GalNAc, trivalent GalNAc or tetravalent GalNAc moieties.

[00167] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5, or 6) nucleotides of the oligonucleotides each can be conjugated to a GalNAc moiety. In some embodiments, 2 to 4 nucleotides of a L each are conjugated to a separate GalNAc. In other embodiments, 1 to 3 nucleotides of a triL each are conjugated to a separate GalNAc. In some embodiments, the targeting ligands are conjugated to 2 to 4 nucleotides at either end of the sense or antisense strand (*e.g.*, ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush, and the oligonucleotides resemble a toothbrush. In some embodiments, the GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, 4 GalNAc moieties are conjugated to nucleotides in the L of the sense strand, where each GalNAc moiety is conjugated to 1 nucleotide. In certain embodiments, 3 GalNAc moieties are conjugated to nucleotides in the L of the sense strand, where each GalNAc moiety is conjugated to 1 nucleotide.

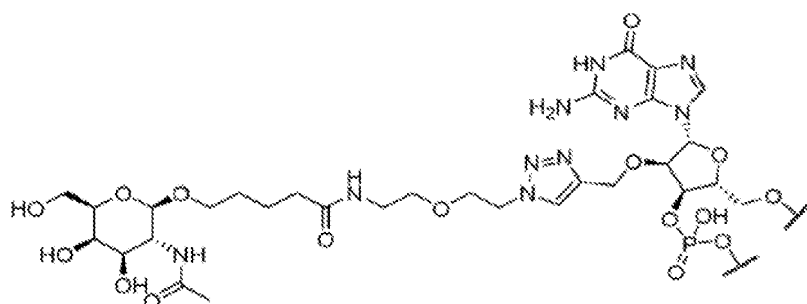
[00168] In certain embodiments, the oligonucleotides comprise a monovalent GalNAc attached to a guanine nucleotide referred to as [ademG-GalNAc] or 2'-aminodiethoxymethanol-Guanine-GalNAc, as depicted below:



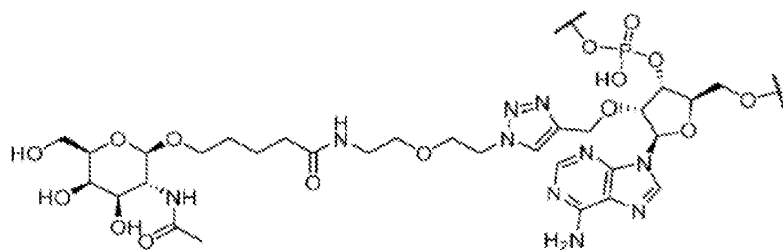
[00169] In certain embodiments, the oligonucleotides herein comprise a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2'-aminodiethoxymethanol-Adenine-GalNAc, as depicted below:



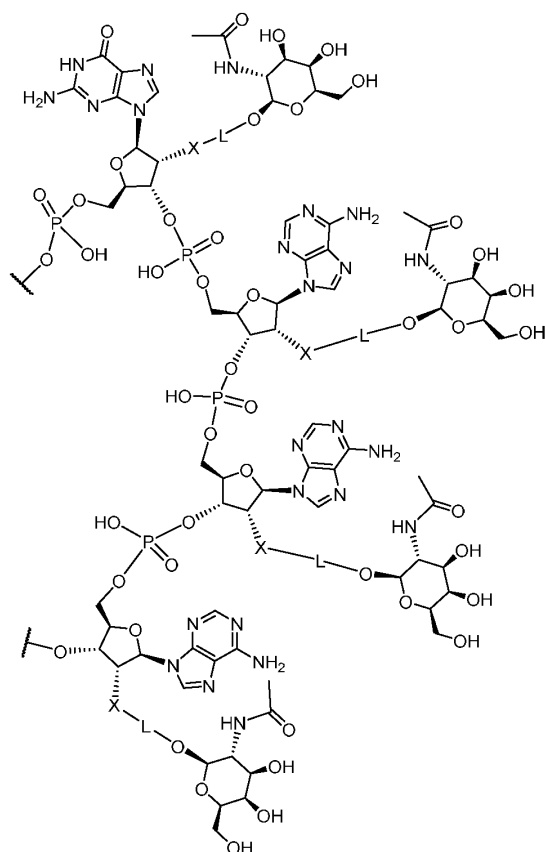
[00170] In certain embodiments, the oligonucleotides comprise a monovalent 2'-GalNAc attached to a guanine nucleotide referred to as [prgG-peg-GalNAc] wherein N-Acetylgalactosamine (GalNAc) is conjugated to guanine via polyethylene glycol and propargyl (alkyne) linker, as depicted below:



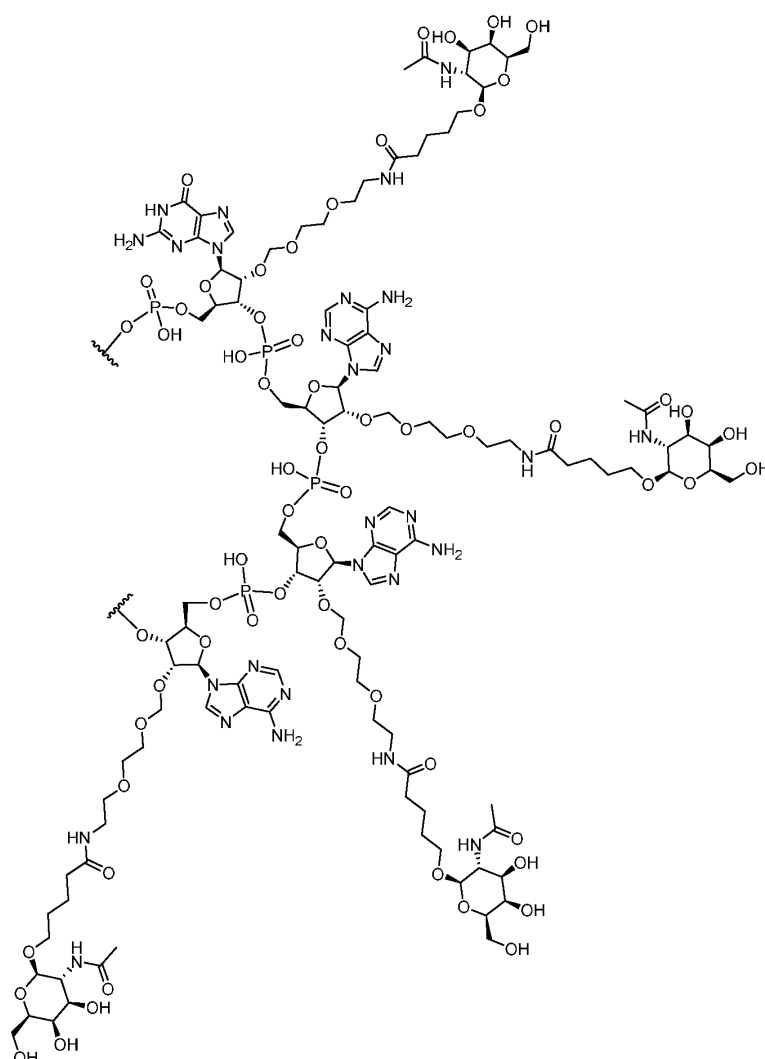
[00171] In certain embodiments, the oligonucleotides herein comprise a monovalent 2'-GalNAc attached to an adenine nucleotide, referred to as [prgA-peg-GalNAc] wherein N-Acetylgalactosamine (GalNAc) is conjugated to adenine via polyethylene glycol and propargyl (alkyne) linker, as depicted below:



[00172] An example of such conjugation is shown below for a loop having from 5' to 3', the nucleotide sequence GAAA (L = linker, X = heteroatom), where stem attachment points are shown. Such a loop is present, for example, at positions 27-30 of the sense strand listed in Table 4 and as shown in FIG. 1. In the chemical formula, $\frac{3}{2}$ is used to describe an attachment point to the oligonucleotide strand:



[00173] Appropriate methods or chemistry (*e.g.*, click chemistry) are used to link a targeting ligand to a nucleotide. One way of conjugating the targeting ligand to a nucleotide is by using a click linker. In some embodiments, an acetal-based linker is used to conjugate the targeting ligand to a nucleotide of any one of the oligonucleotides herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is stable. An example is shown below for a loop having from 5' to 3', the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker. Such a loop is present, for example, at positions 27-30 of the any one of the sense strands listed in Tables 2 or 3. In the chemical formula,  is an attachment point to the oligonucleotide strand:



[00174] In some embodiments, a duplex extension (*e.g.*, of up to 3, 4, 5, or 6 bp in length) is provided between the targeting ligand (*e.g.*, a GalNAc moiety), and the oligonucleotides herein (*e.g.*, a ds oligonucleotide). In other embodiments, the oligonucleotides do not have a GalNAc conjugated thereto.

[00175] Formulations and Pharmaceutical Compositions

[00176] The oligonucleotides herein (*e.g.*, a ds oligonucleotide), or a pharmaceutically acceptable salt thereof (*e.g.*, trifluoroacetate salts, acetate salts or hydrochloride salts), are incorporated into a formulation or pharmaceutical composition. Various formulations have been developed to facilitate oligonucleotide use. For example, oligonucleotides can be

delivered to an individual or a cellular environment using a formulation that minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, the oligonucleotides are formulated in buffer solutions such as phosphate buffered saline solutions, liposomes, micellar structures, and capsids.

[00177] To improve *in vivo* compatibility and effectiveness, the oligonucleotides may be reacted with any of a number of inorganic and organic acids/bases to form pharmaceutically acceptable acid/base addition salts. Pharmaceutically acceptable salts and common methodologies for preparing them are well known in the art (*see, e.g.*, Stahl *et al.*, “Handbook of Pharmaceutical Salts: Properties, Selection and Use,” 2nd Revised Edition (Wiley-VCH, 2011)). Pharmaceutically acceptable salts for use herein include sodium, trifluoroacetate, hydrochloride and acetate salts.

[00178] Formulations of oligonucleotides with cationic lipids are used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (*e.g.*, polylysine) can be used. Suitable lipids include Oligofectamine (ThermoFisher Technologies), Lipofectamine (Life Technologies), NC388 (Ribozyne Pharmaceuticals, Inc.), or FuGene 6 (Roche), all of which are used according to the manufacturer’s instructions.

[00179] Accordingly, in some embodiments, the formulations herein comprise a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere, or a nanoparticle (such as a lipid nanoparticle) or may be otherwise formulated for administration to the cells, tissues, organs, or body of an individual in need thereof (*see, e.g.*, Remington, “The Science and Practice of Pharmacy” (L.V. Allen Jr., ed., 22nd Edition, Pharmaceutical Press, 2013).

[00180] In some embodiments, the formulations herein further comprise an excipient, which can confer to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, the excipient is a buffering agent (*e.g.*, sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.*, a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil). In some embodiments, the oligonucleotides herein are lyophilized for extending shelf-life and then made into a solution before use (*e.g.*, administration to an individual). Accordingly, the excipient in a pharmaceutical composition including one or more of the oligonucleotides is a lyoprotectant (*e.g.*, mannitol, lactose, polyethylene glycol, or polyvinylpyrrolidone) or a collapse temperature modifier (*e.g.*, dextran, Ficoll™, or gelatin).

[00181] Pharmaceutical compositions are formulated to be compatible with its intended route of administration. Routes of administration include, but are not limited to, parenteral (*e.g.*, intravenous, intramuscular, intraperitoneal, intradermal, and subcutaneous), oral (*e.g.*, inhalation), transdermal (*e.g.*, topical), transmucosal, and rectal administration.

[00182] Pharmaceutical compositions suitable for injectable use comprise sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include, but are not limited to, physiological saline, bacteriostatic water, Cremophor EL™ (BASF) or phosphate buffered saline (PBS). The carrier is a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, liquid polyethylene glycol, and the like), as well as suitable mixtures thereof. In many embodiments, it will be preferable to comprise in the compositions with isotonic agents such as, for example, sugars, polyalcohols such as mannitol, sorbitol and/or sodium chloride. Sterile injectable solutions are prepared by incorporating the oligonucleotides herein in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[00183] Moreover, the pharmaceutical compositions comprise at least about 0.1% of a therapeutic agent (*e.g.*, one or more of the oligonucleotides herein) or more, although the percentage of the therapeutic agent may be between about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one of skill in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

[00184] Even though several examples are directed toward liver-targeted delivery of at least one of the oligonucleotides herein, targeting of other tissues also is contemplated.

[00185] Kits

[00186] The oligonucleotides herein (*e.g.*, a ds oligonucleotide) can be incorporated into a kit comprising one or more of the oligonucleotides herein, and instructions for use. In some embodiments, the kit comprises one or more of the oligonucleotides, and a package insert containing instructions for use of the kit and/or any component thereof. In other embodiments, the kit comprises a suitable container, one or more of the oligonucleotides, one or more controls, and various buffers, reagents, enzymes, and other standard ingredients as are known in the art.

[00187] In some embodiments, the container can be at least one vial, well, test tube, flask, bottle, syringe, or other container means, into which the one or more oligonucleotides are placed, and in some embodiments, suitably aliquoted. In other embodiments, where an additional component is provided, the kit contains additional containers into which this component is placed. The kit also comprises a means for containing the one or more oligonucleotides and any other reagent in close confinement for commercial sale. Such containers include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits comprise labeling with instructions for use and/or warnings.

[00188] In some embodiments, the kit comprises one or more oligonucleotides herein, and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising one or more of the oligonucleotides and instructions for treating or delaying progression of a disease, disorder, or condition associated with *APOC3* expression in an individual in need thereof.

Methods

[00189] Methods of Making

[00190] The oligonucleotides herein (*e.g.*, a ds oligonucleotide) are made using methods and/or techniques known to one of skill in the art such as, for example, conventional nucleic acid solid phase synthesis. The polynucleotides of the oligonucleotides are assembled on a suitable nucleic acid synthesizer utilizing standard nucleotide or nucleoside precursors (*e.g.*, phosphoramidites). Automated nucleic acid synthesizers, including DNA/RNA synthesizers, are commercially available from, for example, Applied Biosystems (Foster City, CA), BioAutomation (Irving, TX), and GE Healthcare Life Sciences (Pittsburgh, PA).

[00191] As one of skill in the art understands, other methods and/or techniques of synthesizing the oligonucleotides herein are used. Additionally, the various synthetic steps are performed in an alternate sequence or order to give the desired compounds. Other synthetic chemistry transformations, protecting groups (*e.g.*, for hydroxyl, amino, *etc.* present on the bases), and protecting group methodologies (protection and deprotection) useful in synthesizing the oligonucleotides are known in the art and are described in, for example, Larock, "Comprehensive Organic Transformations," VCH Publishers (1989); Greene & Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 2nd Ed., John Wiley & Sons (1991); Fieser & Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley & Sons (1994); and Paquette, ed., ENCYCLOPEDIA OF REAGENTS FOR ORGANIC SYNTHESIS, John Wiley & Sons (1995).

[00192] Methods of Using

[00193] I. Methods of Reducing *APOC3* Expression in Cells, Tissue, Organs, and Organisms: The oligonucleotides herein (*e.g.*, a ds oligonucleotide) are used to reduce *APOC3* mRNA in cells, tissues, organs, or individuals. The methods comprise the steps described herein, and these may be, but not necessarily, carried out in the sequence as described. Other sequences, however, also are conceivable. Moreover, individual, or multiple steps are carried out either in parallel and/or overlapping in time and/or individually or in multiply repeated steps. Furthermore, the methods comprise additional, unspecified steps.

[00194] The methods comprise contacting or delivering to a cell, population of cells, tissues, organs, or individuals an effective amount any of the oligonucleotides herein for reducing *APOC3* expression. In some embodiments, reduced *APOC3* expression is determined by measuring a reduction in the amount or level of *APOC3* mRNA, *APOC3* protein, or *APOC3* activity in a cell.

[00195] With regard to an appropriate cell type, the cell type is any cell that expresses mRNA (*e.g.*, hepatocytes, macrophages, monocyte-derived cells, prostate cancer cells, cells of the brain, endocrine tissue, bone marrow, lymph nodes, lung, gall bladder, liver, duodenum, small intestine, pancreas, kidney, gastrointestinal tract, bladder, adipose and soft tissue, and skin). In some embodiments, the cell is a primary cell obtained from an individual. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains its natural phenotypic properties. In some embodiments, the cell is an *ex vivo*, *in vivo*, or *in vitro* cell (*i.e.*, such that one or more of the oligonucleotides herein can be delivered to the cell in culture or to an organism in which the cell resides).

[00196] In some embodiments, the oligonucleotides herein are delivered to a cell or population of cells using a nucleic acid delivery method known in the art including, but not limited to, injecting a solution containing the oligonucleotides, bombarding by particles covered by the oligonucleotides, exposing the cell or population of cells to a solution containing the oligonucleotides, or electroporating cell membranes in the presence of the oligonucleotides. Other methods known in the art for delivering oligonucleotides to cells are used such as, for example, lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[00197] Reduced *APOC3* expression is determined by an assay or technique that evaluates one or more molecules, properties or characteristics of a cell or population of cells associated with *APOC3* expression (*e.g.*, using an *APOC3* expression biomarker) or by an assay or

technique that evaluates molecules that are directly indicative of *APOC3* expression in a cell or population of cells (*e.g.*, *APOC3* mRNA or *APOC3* protein). In some embodiments, the extent to which the oligonucleotides reduce *APOC3* expression are evaluated by comparing *APOC3* expression in a cell or population of cells contacted with the oligonucleotides to a control cell or population of cells (*e.g.*, a cell or population of cells not contacted with the oligonucleotides or contacted with a control oligonucleotide). In some embodiments, a control amount or level of *APOC3* expression in a control cell or population of cells is predetermined, such that the control amount or level need not be measured in every instance the assay or technique is performed. The predetermined level or value takes a variety of forms including, but not limited to, a single cut-off value, such as a median or mean.

[00198] Contacting or delivering the oligonucleotides herein to a cell or a population of cells result in reduced *APOC3* expression. In some embodiments, reduced *APOC3* expression is relative to a control amount or level of *APOC3* expression in the cell or the population of cells not contacted with the oligonucleotides or contacted with a control oligonucleotide. In some embodiments, reduced *APOC3* expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of *APOC3* expression. In some embodiments, the control amount or level of *APOC3* expression is an amount or level of *APOC3* mRNA and/or *APOC3* protein in the cell or the population of cells that has not been contacted with oligonucleotides herein. In some embodiments, the effect of delivery of the oligonucleotides to the cell or the population of cells according to a method herein is assessed after any finite period or amount of time (*e.g.*, minutes, hours, days, weeks, and/or months). For example, *APOC3* expression is determined in the cell or the population of cells at least about 4 hours, about 8 hours, about 12 hours, about 18 hours, or about 24 hours. Alternatively, *APOC3* expression is determined in the cell or the population of cells at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, about 56 days, about 63 days, about 70 days, about 77 days, or about 84 days or more after contacting or delivering the oligonucleotides to the cell or population of cells. In other embodiments, *APOC3* expression is determined in the cell or the population of cells at least about 1 month, about 2 months, about 3 months, about 4 months,

about 5 months, or about 6 months or more after contacting or delivering the oligonucleotides to the cell or the population of cells.

[00199] In some embodiments, the oligonucleotides herein are delivered in the form of a transgene that is engineered to express in a cell one or more of the oligonucleotides or strands (*e.g.*, sense and antisense strands). For example, the oligonucleotides are delivered using a transgene engineered to express any oligonucleotide herein. Transgenes may be delivered using viral vectors (*e.g.*, adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus, or herpes simplex virus) or non-viral vectors (*e.g.*, plasmids or synthetic mRNAs). In some embodiments, the transgenes are injected directly to an individual.

[00200] II. Methods of Treatment: Methods of treating an individual having, suspected of having or at risk of developing, a disease, disorder, or condition associated with *APOC3* expression comprise administering at least one or more of the oligonucleotides herein (*e.g.*, a ds oligonucleotide) to the individual. Additionally, methods of treating or attenuating an onset or progression of a disease, disorder, or condition associated with *APOC3* expression in an individual comprise using one or more of the oligonucleotides herein. Furthermore, methods of achieving one or more therapeutic benefits in an individual having a disease, disorder, or condition associated with *APOC3* expression comprise providing one or more of the oligonucleotides herein. In some embodiments, the individual can be treated by administering a therapeutically effective amount of any one or more of the oligonucleotides herein. In some embodiments, the treatment comprises reducing *APOC3* expression. In some embodiments, the individual is treated therapeutically. In some embodiments, the individual is treated prophylactically. In all these embodiments, the oligonucleotide is selected from Table 3.

[00201] In some embodiments, the one or more oligonucleotides, or a pharmaceutical composition including the same, is administered to the individual having a disease, disorder, or condition associated with *APOC3* expression such that *APOC3* expression is reduced in the individual, thereby treating the individual. In some embodiments, an amount or level of *APOC3* mRNA is reduced in the individual. In other embodiments, an amount or level of *APOC3* protein is reduced in the individual. In still other embodiments, an amount or level of *APOC3* activity is reduced in the individual. In yet other embodiments, an amount or level of liver TG (*e.g.*, one or more TG(s) or total TGs in liver) is reduced in the individual, especially in the liver. In still other embodiments, an amount or level of liver inflammation can be reduced. In still other embodiments, an amount or level of liver fibrosis is reduced. In still other embodiments, an amount or level of plasma aspartate aminotransferase (AST), plasma alanine

aminotransferase (ALT), Cytokeratin 18 (CK-18), or even N-terminal type III collagen propeptide (Pro-C3) is reduced. In any of the above disclosed embodiments, the oligonucleotides comprise a sense strand having a nucleotide sequence of any one of SEQ ID NOs:143, 149, 151, 193, 195, 205, 207 and 211, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs:144, 150, 152, 194, 196, 206, 208 and 212.

[00202] In some embodiments, *APOC3* expression is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to *APOC3* expression prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In other embodiments, *APOC3* expression is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to *APOC3* expression in an individual (*e.g.*, a reference or control individual) not receiving the one or more oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[00203] In certain embodiments, an amount or level of *APOC3* mRNA is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of *APOC3* mRNA prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In some embodiments, the amount or level of *APOC3* mRNA is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of *APOC3* mRNA in an individual (*e.g.*, a reference or control individual) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition, or treatment.

[00204] In certain embodiments, an amount or level of *APOC3* protein is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of *APOC3* protein prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In

other embodiments, an amount or level of APOC3 protein is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of APOC3 protein in an individual (*e.g.*, a reference or control individual) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition or treatment.

[00205] In certain embodiments, an amount or level of APOC3 activity is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of APOC3 activity prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In some embodiments, the amount or level of APOC3 activity is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of APOC3 activity in an individual (*e.g.*, a reference or control individual) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition or treatment.

[00206] In certain embodiments, an amount or level of TG, especially liver TG, can be reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of TG prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In some embodiments, the amount or level of TG is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of TG in an individual (*e.g.*, a reference or control individual) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition or treatment.

[00207] Here, *APOC3* expression, the amount or level of *APOC3* mRNA, *APOC3* protein, *APOC3* activity, liver TG, or any combination thereof, is reduced in a cell (*e.g.*, a hepatocyte), a population or a group of cells (*e.g.*, an organoid), a tissue (*e.g.*, liver tissue), a sample (*e.g.*, a

liver biopsy sample), an organ (*e.g.*, liver), blood or a fraction thereof (*e.g.*, plasma), or any other biological material obtained or isolated from the individual. In some embodiments, *APOC3* expression, the amount or level of *APOC3* mRNA, *APOC3* protein, *APOC3* activity, TG, or any combination thereof, is reduced in more than one type of cell (*e.g.*, a hepatocyte and one or more other type(s) of cell), more than one groups of cells, more than one type of tissue (*e.g.*, liver tissue and one or more other type(s) of tissue), more than one type of sample (*e.g.*, a liver biopsy sample and one or more other type(s) of biopsy sample), more than one organ (*e.g.*, liver and one or more other organ(s)), more than one fraction of blood (*e.g.*, plasma and one or more other blood fraction(s)) obtained or isolated from the individual.

[00208] Examples of a disease, disorder, or condition associated with *APOC3* expression include, but are not limited to, ACD, AH, ALD, ASCVD, HCC, CHD, CCA, PSC, MetS, NAFLD, NASH, high non-HDL cholesterol, hyperlipidemia, hypertriglyceridemia, diabetes, obesity, fatty liver (steatosis), inflammation of the liver, insulin resistance, liver fibrosis, cirrhosis of the liver, or a combination thereof.

[00209] Because of their high specificity, the oligonucleotides herein specifically target mRNAs of target genes of cells, tissues, or organs (*e.g.*, liver). In preventing disease, the target gene is the one that is required for initiation or maintenance of the disease or that has been identified as being associated with a higher risk of contracting the disease. In treating disease, one or more of the oligonucleotides herein are brought into contact with the cells, tissue or organ exhibiting or responsible for mediating the disease. For example, an oligonucleotide substantially identical to all or part of a wild-type (*i.e.*, native) or mutated gene associated with a disorder or condition associated with *APOC3* expression is brought into contact with or introduced into a cell or tissue type of interest such as a hepatocyte or other liver cell.

[00210] In some embodiments, the target gene is from any mammal, such as a human. Any gene may be silenced according to the methods herein. Moreover, the methods herein typically involve administering to an individual a therapeutically effective amount of one or more oligonucleotides herein, that is, an amount capable of producing a desirable therapeutic result. The therapeutically acceptable amount is an amount that therapeutically treats a disease or disorder or condition. The appropriate dosage for any one individual will depend on certain factors, including the individual's size, body surface area, age, the composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other therapeutic agents being administered concurrently.

[00211] In the methods, the individual is administered any one of the oligonucleotides or compositions herein either enterally (*e.g.*, orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy, or rectally), parenterally (*e.g.*, subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, or intrathecal), topically (*e.g.*, epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (*e.g.*, the liver of an individual). Typically, the oligonucleotides or compositions are administered intravenously or subcutaneously.

[00212] As a non-limiting set of examples, the oligonucleotides or compositions herein typically are administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the oligonucleotides or compositions are administered every week or at intervals of two, or three weeks. In certain embodiments, the oligonucleotides, or compositions are administered daily. In some embodiments, an individual is administered one or more loading doses of the oligonucleotides or compositions followed by one or more maintenance doses of the oligonucleotides or compositions.

[00213] In some embodiments, the individual is a human, a NHP, or other mammalian individual. In other embodiments, the individual is a domesticated animal such as a dog or a cats; livestock such as a horse, cattle, pig, sheep, goat, or chicken; and animals such as a mouse, rat, guinea pig or hamster.

[00214] III. Medical Uses: The oligonucleotides herein (*e.g.*, a ds oligonucleotide) can be used, or adapted for use, to treat an individual (*e.g.*, a human having a disease, disorder, or condition associated with *APOC3* expression) that would benefit from reducing *APOC3* expression. In some embodiments, the oligonucleotides are provided for use, or adapted for use, to treat an individual having a disease, disorder, or condition associated with *APOC3* expression. Also, the oligonucleotides are provided for use, or adaptable for use, in the manufacture of a medicament or pharmaceutical composition for treating a disease, disorder, or condition associated with *APOC3* expression. In other embodiments, the oligonucleotides are provided for use, or adaptable for use, in targeting *APOC3* mRNA and reducing *APOC3* expression (*e.g.*, *via* the RNAi pathway). In other embodiments, the oligonucleotides are provided for use, or adaptable for use, in targeting *APOC3* mRNA and reducing an amount or level of *APOC3* mRNA, *APOC3* protein, and/or *APOC3* activity.

[00215] In some embodiments, the methods comprise selecting an individual for treatment based upon the individual having a marker (*e.g.*, a biomarker) for a disease, disorder, or

condition associated with *APOC3* expression, or someone predisposed to the same, such as, but not limited to, *APOC3* mRNA, *APOC3* protein or a combination thereof. Likewise, and as detailed below, the methods also comprise additional steps such as, for example, measuring or obtaining a baseline value for a marker of *APOC3* expression (*e.g.*, *APOC3* protein) and then comparing such obtained value to one or more other baseline values or values obtained after the individual is administered one or more of the oligonucleotides to assess the effectiveness of treatment.

EXAMPLES

[00216] The following non-limiting examples are offered for purposes of illustration, not limitation.

[00217] SYNTHESIS OF OLIGONUCLEOTIDES

[00218] Example 1: Preparing ds RNAi Oligonucleotides

[00219] *Oligonucleotide synthesizing and purifying:* The ds RNAi oligonucleotides in the Examples are chemically synthesized using methods described herein. Generally, ds RNAi oligonucleotides are synthesized using solid phase oligonucleotide synthesis methods as described for 19-23mer siRNAs (*see, e.g.*, Scaringe *et al.* (1990) NUCLEIC ACIDS RES. 18:5433-41 and Usman *et al.* (1987) J. AM. CHEM. SOC. 109:7845-45; *see also*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,008,400; 6,111,086; 6,117,657; 6,353,098; 6,362,323; 6,437,117 and 6,469,158).

[00220] Individual RNA strands are synthesized and HPLC purified according to standard methods (Integrated DNA Technologies). For example, RNA oligonucleotides are synthesized using solid phase phosphoramidite chemistry, deprotected, and desalted on NAP-5 columns (Amersham Pharmacia Biotech; Piscataway, NJ) using standard techniques (Damha & Olgivie (1993) METHODS MOL. BIOL. 20:81-114; Wincott *et al.* (1995) NUCLEIC ACIDS RES. 23:2677-84). The oligomers are purified using ion-exchange high performance liquid chromatography (IE-HPLC) on an Amersham Source 15Q column (1.0 cm×25 cm; Amersham Pharmacia Biotech) using a 15 min step-linear gradient. The gradient varies from 90:10 Buffers A:B to 52:48 Buffers A:B, where Buffer A is 100 mM Tris pH 8.5 and Buffer B is 100 mM Tris pH 8.5, 1 M NaCl. Samples are monitored at 260 nm and peaks corresponding to the full-length oligonucleotide species are collected, pooled, desalted on NAP-5 columns, and lyophilized.

[00221] The purity of each oligomer is determined by capillary electrophoresis (CE) on a Beckman PACE 5000 (Beckman Coulter, Inc.). The CE capillaries have a 100 μ m inner diameter and contain ssDNA 100R Gel (Beckman-Coulter). Typically, about 0.6 nmole of oligonucleotide is injected into a capillary, is run in an electric field of 444 V/cm, and is detected by UV absorbance at 260 nm. Denaturing Tris-Borate-7 M-urea running buffer is purchased from Beckman-Coulter. Oligoribonucleotides are obtained that are at least 90% pure as assessed by CE for use in experiments described below. Compound identity is verified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy on a Voyager DE™ Biospectrometry Work Station (Applied Biosystems) following the manufacturer's recommended protocol. Relative molecular masses of all oligomers are obtained, often within 0.2% of expected molecular mass.

[00222] *Preparing duplexes:* ss RNA oligomers are resuspended (*e.g.*, at 100 μ M concentration) in duplex buffer having 100 mM potassium acetate, 30 mM HEPES, pH 7.5. Complementary sense and antisense strands are mixed in equal molar amounts to yield a final solution of, for example, 50 μ M duplex. Samples are heated to 100°C for 5 min in RNA buffer (IDT) and are allowed to cool to room temperature before use. The ds RNA oligonucleotides are stored at -20°C. ss RNA oligomers are stored lyophilized or in nuclease-free water at -80°C.

[00223] *IN VITRO FUNCTION*

[00224] Example 2: RNAi Oligonucleotide Inhibition of *APOC3* Expression *In Vitro* – DsiRNA-Based Compounds

[00225] *APOC3 target sequence identifying:* To identify RNAi oligonucleotide inhibitors of *APOC3* expression, a computer-based algorithm is used to computationally generate *APOC3* target sequences suitable for assaying *APOC3* expression inhibition by the RNAi pathway. The algorithm provides RNAi oligonucleotide antisense (guide) strand sequences that are complementary to suitable *APOC3* target sequences of human *APOC3* mRNA (*e.g.*, SEQ ID NO:1). Some of the antisense strand sequences identified by the algorithm also are complementary to the corresponding *APOC3* target sequence of NHP *APOC3* mRNA (*e.g.*, monkey, SEQ ID NO:5). From this, 384 ds RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) are generated, each with a unique antisense strand having a region of complementarity to a *APOC3* target sequence identified by the algorithm.

[00226] *In vitro cell-based assays:* The ability of each of the 384 DsiRNAs to inhibit *APOC3* expression is determined *via in vitro* cell-based assays. Further, and as shown herein, the

nucleotide sequences for the passenger strand and guide strand of the DsiRNAs a distinct pattern of modified nucleotides and phosphorothioate linkages. Briefly, Hep G2 cells stably expressing *APOC3* are transfected with each of the DsiRNAs (0.5 nM) in separate wells of a multi-well cell culture plate. Cells are maintained for 24 hr following transfection, and then levels of remaining *APOC3* mRNA from the transfected cells are determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3' assay and a 5' assay, are used to determine mRNA levels as measured by HEX probes.

[00227] The results of the Hep G2 cell-based assay with the 384 DsiRNAs are shown in Table 1, where the 384 DsiRNAs have guide strands that are complementary to human and NHP *APOC3* mRNA (“double-common”). Transfection of a double-common DsiRNA that results in less than or equal to 30% *APOC3* mRNA remaining in the cells when compared to negative controls is considered a candidate *APOC3* expression inhibitor (referred to herein as a “hit”).

[00228] Table 1: Double-Common DsiRNA *APOC3* Knockdown in Hep G2 Cells, 0.5 nM 24 hr-5'and -3' Assays % mRNA Remaining (normalized to hSFRS9-F569(HEX) vs Mock Control).

DsiRNA	APOC3-F149	
	% mRNA Remaining	% SEM
1	35.2	2.5
2	55.3	1.7
3	43.3	4.4
4	41.7	3.2
5	39.7	4.5
6	53.0	1.2
7	47.0	3.0
8	41.3	2.5
9	53.8	1.5
10	44.2	3.8
11	45.0	2.2
12	55.1	4.8
13	56.1	1.1
14	23.3	1.3
15	28.3	1.3
16	34.9	3.6
17	33.3	2.2
18	47.3	3.2
19	65.4	5.6
20	41.0	7.1
21	41.6	3.1
22	34.3	2.4

23	31.0	2.0
24	56.9	4.4
25	48.9	2.3
26	49.7	5.7
27	41.4	3.5
28	43.3	3.9
29	49.6	2.0
30	70.3	2.2
31	42.0	1.7
32	60.0	3.6
33	50.8	1.5
34	34.3	2.0
35	38.5	3.8
36	54.0	3.3
37	58.9	6.4
38	58.9	2.8
39	52.1	2.4
40	60.3	5.2
41	69.0	3.0
42	44.7	5.5
43	36.8	1.8
44	35.5	1.5
45	37.4	1.7
46	38.1	1.4
47	36.9	2.8
48	52.4	2.1
49	32.1	2.2
50	29.8	1.5
51	36.5	1.9
52	34.9	3.5
53	45.9	2.4
54	41.8	2.5
55	33.5	5.6
56	38.6	6.6
57	15.7	0.9
58	164.0	6.1
59	32.1	5.2
60	120.3	10.1
61	40.4	1.9
62	38.2	1.6
63	36.1	2.6
64	42.0	2.2
65	62.1	3.6
66	63.0	2.1
67	65.9	1.8
68	121.6	4.4
69	72.6	11.2

70	112.5	7.2
71	57.3	2.9
72	66.1	3.8
73	59.7	3.5
74	85.9	5.3
75	75.5	4.3
76	38.6	4.1
77	46.4	5.9
78	24.7	3.6
79	42.0	4.3
80	38.5	4.1
81	51.8	5.2
82	26.7	5.7
83	19.5	1.3
84	39.0	3.8
85	42.6	2.7
86	37.4	2.8
87	34.4	7.4
88	38.4	3.0
89	37.9	2.2
90	24.9	1.0
91	43.4	3.0
92	29.6	1.8
93	31.8	1.5
94	59.1	2.6
95	101.6	5.0
96	56.7	6.9
97	97.6	9.6
98	50.3	5.3
99	26.0	4.8
100	20.8	3.5
101	20.4	2.2
102	73.0	6.0
103	96.4	3.3
104	48.3	1.9
105	143.5	7.0
106	105.8	8.6
107	102.9	8.7
108	95.5	1.3
109	99.7	6.7
110	46.6	5.2
111	44.2	2.5
112	49.4	5.5
113	61.3	2.9
114	71.5	4.3
115	98.0	3.9
116	42.2	3.8

117	30.8	1.0
118	40.2	3.1
119	34.2	1.0
120	24.7	1.8
121	26.4	4.0
122	21.0	3.3
123	28.0	2.6
124	52.8	1.8
125	160.2	3.9
126	49.4	6.9
127	52.5	2.4
128	46.9	2.5
129	30.6	1.2
130	28.2	1.3
131	32.0	3.5
132	37.3	3.2
133	31.9	2.7
134	29.8	3.2
135	31.5	4.2
136	73.9	3.7
137	30.5	3.5
138	88.9	1.7
139	40.1	1.2
140	39.2	3.4
141	41.2	2.0
142	40.9	2.7
143	141.5	4.8
144	30.4	3.3
145	43.5	2.6
146	55.5	7.9
147	16.6	1.1
148	13.0	1.8
149	63.0	2.3
150	44.6	3.1
151	31.6	2.3
152	19.5	1.9
153	31.7	1.3
154	38.5	5.2
155	18.9	1.1
156	39.5	1.1
157	89.0	2.7
158	43.5	2.4
159	27.2	1.5
160	21.8	0.9
161	53.2	2.6
162	46.4	5.1
163	92.4	2.2

164	30.3	1.9
165	53.7	5.2
166	21.7	2.5
167	27.1	1.6
168	49.7	5.5
169	31.1	1.4
170	39.7	3.2
171	45.3	2.3
172	71.7	6.1
173	45.2	4.4
174	37.9	3.2
175	27.5	1.8
176	34.5	1.0
177	37.6	3.7
178	41.7	2.7
179	40.4	2.9
180	59.2	1.5
181	32.9	1.3
182	27.8	3.6
183	31.5	2.6
184	28.8	5.5
185	32.7	4.0
186	37.5	4.6
187	30.9	7.0
188	38.9	5.0
189	33.3	1.0
190	21.9	1.7
191	28.9	2.1
192	30.8	1.8
193	29.0	2.1
194	26.0	1.7
195	23.9	1.4
196	26.6	4.0
197	26.0	2.7
198	28.4	1.3
199	39.8	2.9
200	41.6	3.2
201	21.7	0.5
202	21.9	2.7
203	42.6	2.4
204	38.2	1.7
205	33.4	2.6
206	30.2	2.5
207	47.7	3.4
208	28.4	2.2
209	76.2	6.7
210	160.5	16.9

211	217.8	6.5
212	47.6	3.3
213	110.8	5.7
214	74.8	6.2
215	66.8	4.1
216	45.3	2.0
217	62.2	4.0
218	34.7	1.4
219	67.2	2.6
220	54.9	3.1
221	51.4	1.1
222	63.4	7.4
223	60.2	1.7
224	96.9	4.4
225	113.8	1.8
226	65.4	5.9
227	40.3	3.0
228	138.4	12.1
229	76.3	25.6
230	48.9	5.1
231	50.2	3.3
232	79.6	1.6
233	63.6	2.4
234	69.4	5.8
235	96.0	6.8
236	121.6	3.0
237	46.9	2.6
238	30.9	1.5
239	50.8	3.6
240	68.4	3.8
241	50.4	1.8
242	27.4	1.1
243	33.8	1.2
244	29.6	1.8
245	67.1	3.4
246	28.0	1.3
247	43.4	5.9
248	20.7	2.1
249	40.2	3.4
250	57.6	2.4
251	55.1	4.5
252	58.3	5.4
253	60.4	4.5
254	56.4	6.3
255	24.2	2.4
256	32.0	1.0
257	61.9	1.2

258	87.5	3.3
259	40.2	0.9
260	55.8	3.0
261	32.1	2.1
262	31.4	2.9
263	26.4	1.6
264	11.3	0.8
265	16.3	1.3
266	62.7	3.4
267	10.9	0.6
268	10.4	0.9
269	12.5	1.1
270	19.9	0.7
271	13.7	1.6
272	17.0	1.0
273	14.6	0.8
274	61.4	2.9
275	15.1	1.0
276	21.2	1.4
277	31.7	2.0
278	109.0	12.6
279	75.2	4.1
280	30.8	2.8
281	31.2	3.7
282	27.2	1.8
283	16.2	1.0
284	40.4	2.8
285	21.5	1.3
286	18.7	0.7
287	17.2	1.7
288	47.5	5.1
289	47.5	5.8
290	35.7	1.3
291	53.3	3.1
292	63.2	9.7
293	52.8	5.3
294	25.7	1.5
295	59.8	4.2
296	59.6	6.2
297	44.8	5.7
298	36.0	1.3
299	50.2	5.3
300	30.5	1.7
301	23.7	0.7
302	62.7	8.6
303	88.9	8.3
304	111.2	7.0

305	162.1	17.5
306	101.8	11.3
307	81.2	6.2
308	110.4	5.8
309	73.2	7.8
310	68.0	1.5
311	119.5	11.6
312	91.7	9.8
313	60.2	6.5
314	70.1	8.2
315	50.1	3.6
316	36.6	2.8
317	61.7	4.3
318	43.2	4.4
319	13.1	9.4
320	39.0	3.0
321	36.4	2.3
322	45.2	2.6
323	30.6	2.3
324	42.1	4.7
325	46.1	1.5
326	35.3	4.8
327	32.3	2.0
328	26.1	3.5
329	35.2	2.4
330	23.4	2.7
331	27.6	1.8
332	25.6	2.1
333	24.6	3.7
334	27.7	0.4
335	20.8	1.7
336	20.5	1.4
337	28.3	2.7
338	22.6	1.1
339	26.9	1.9
340	28.8	2.1
341	107.9	3.2
342	24.1	3.9
343	57.8	3.0
344	46.1	4.6
345	42.7	2.8
346	30.2	4.0
347	31.1	3.7
348	45.6	3.1
349	27.6	1.8
350	87.1	6.6
351	78.0	2.2

352	106.0	5.4
353	111.1	4.7
354	96.5	4.6
355	33.1	1.9
356	97.4	3.2
357	55.8	2.1
358	86.5	2.2
359	106.4	5.6
360	90.5	4.4
361	93.7	2.9
362	100.5	7.5
363	65.7	3.5
364	63.0	2.6
365	78.2	6.0
366	55.2	2.7
367	45.8	9.4
368	54.6	2.0
369	42.6	2.2
370	35.4	3.4
371	31.8	0.5
372	31.3	1.8
373	41.1	2.3
374	58.5	2.1
375	45.5	2.8
376	36.3	4.5
377	31.8	1.5
378	37.7	2.1
379	29.2	2.1
380	29.6	1.7
381	31.2	2.0
382	32.7	2.0
383	43.9	3.7
384	23.7	1.6

[00229] These results show that DsiRNAs designed to target human APOC3 mRNA inhibit *APOC3* expression in cells (as determined by a reduced amount of APOC3 mRNA in DsiRNA-transfected cells) and that the nucleotide sequences including the DsiRNA hits are useful for generating RNAi oligonucleotides to inhibit *APOC3* expression. Further, these results demonstrate that multiple APOC3 target sequences are suitable for the RNAi-mediated inhibition of *APOC3* expression.

[00230] Example 3: RNAi Oligonucleotide Inhibition of *APOC3* Expression *In Vitro* – GalXC-Based Compounds

[00231] Of the 384 DsiRNAs screened in the Hep G2 cell-based assays described in Example 2, the nucleotide sequences of 81 DsiRNAs hits are selected for evaluation *in vitro* as GalXC-based compounds. Briefly, the nucleotide sequences the selected DsiRNAs are used to generate 53 corresponding ds RNAi oligonucleotides including a nicked tetraloop GalNAc-conjugated structure (referred to herein as “GalXC APOC3 oligonucleotides”) having a 36-mer sense (passenger) strand and a 22-mer antisense (guide) strand. Further, the nucleotide sequences for the sense strand and antisense strand of the GalXC APOC3 oligonucleotides have a distinct pattern of modified nucleotides and phosphorothioate linkages (*see, e.g.*, FIGS. 1A-1C for a schematic of the generic structure and chemical modification patterns of the GalXC APOC3 oligonucleotides). The three adenosine nucleotides of the tetraloop each are conjugated to a GalNAc moiety (CAS#: 14131-60-3). Further, the nucleotide sequences for the sense strand and antisense strand of the GalXC APOC3 oligonucleotides have one of three distinct patterns of modified nucleotides and phosphorothioate linkages (*see, e.g.*, FIGS. 1A-1C), although exemplary modification patterns are shown in Table 3.

[00232] Table 2: GalXC-APOC3 Oligonucleotides (unmodified).

GalXC-APOC3	Sense Strand (passenger; 36-mer)	SEQ ID NO:	Antisense Strand (guide; 22-mer)	SEQ ID NO:
1	CUAGAGGCAGCUGC UCCAGAGCAGCCGA AAGGCUGC	9	UCUGGAGCAGCUGCCU CUAGGG	10
2	GGUACUCCUUGUUG UUGCCAGCAGCCGA AAGGCUGC	11	UGGCAACAACAAGGAG UACCGG	12
3	GAGGCCGAGGAUGC CUCCAGCAGCCGA AAGGCUGC	13	UGGGAGGCAUCCUCGG CCUCGG	14
4	CCUUCUCAGCUUCA UGCAGAGCAGCCGA AAGGCUGC	15	UCUGCAUGAAGCUGAG AAGGGG	16
5	CUUCUCAGCUUCAU GCAGGAGCAGCCGA AAGGCUGC	17	UCCUGCAUGAAGCUGA GAAGGG	18
6	CUCAGCUUCAUGCA GGGUUAGCAGCCGA AAGGCUGC	19	UAACCCUGCAUGAAGC UGAGGG	20
7	AUGCACUGAGCAGC GUGCAAGCAGCCGA AAGGCUGC	21	UUGCACGCUGCUCAGU GCAUGG	22
8	UGCACUGAGCAGCG UGCAGAGCAGCCGA AAGGCUGC	23	UCUGCACGCUGCUCAG UGCAGG	24

9	CUGAGCAGCGUGCA GGAGUAGCAGCCGA AAGGCUGC	25	UACUCCUGCACGCUGC UCAGGG	26
10	AGCAGCGUGCAGGA GUCCCAGCAGCCGA AAGGCUGC	27	UGGGACUCCUGCACGC UGCUGG	28
11	UGCAGGAGUCCCAG GUGGCAGCAGCCGA AAGGCUGC	29	UGCCACCUGGGACUCC UGCAGG	30
12	GGGGCUGGGUGACC GAUGGAGCAGCCGA AAGGCUGC	31	UCCAUCGGUCACCCAGC CCCGG	32
13	GGCUUCAGUUCCCU GAAAGAGCAGCCGA AAGGCUGC	33	UCUUUCAGGGAACUGA AGCCGG	34
14	CUUCAGUUCCCUGA AAGACAGCAGCCGA AAGGCUGC	35	UGUCUUUCAGGGAACU GAAGGG	36
15	UUCAGUUCCUGAA AGACUAGCAGCCGA AAGGCUGC	37	UAGUCUUUCAGGGAAC UGAAGG	38
16	AGACUACUGGAGCA CCGUUAGCAGCCGA AAGGCUGC	39	UAACGGUGCUCCAGUA GUCUGG	40
17	UACUGGAGCACCGU UAAGGAGCAGCCGA AAGGCUGC	41	UCCUUAACGGUGCUCC AGUAGG	42
18	UGGAGCACCGUUA GGACAAGCAGCCGA AAGGCUGC	43	UUGUCCUUAACGGUGC UCCAGG	44
19	ACCGUUAAGGACAA GUUCUAGCAGCCGA AAGGCUGC	45	UAGAACUUGUCCUUA CGGUGG	46
20	CCGUUAAGGACAAG UUCUCAGCAGCCGA AAGGCUGC	47	UGAGAACUUGUCCUUA ACGGGG	48
21	CGUUAAGGACAAGU UCUCUAGCAGCCGA AAGGCUGC	49	UAGAGAACUUGUCCUU AACGGG	50
22	GUUAAGGACAAGU UCUCUGAGCAGCCG AAAGGCUGC	51	UCAGAGAACUUGUCCU UAACGG	52
23	AGGACAAGUUCUCU GAGUUAGCAGCCGA AAGGCUGC	53	UAACUCAGAGAACUUG UCCUGG	54
24	AGGACAAGUUCUCU GAGUUAGCAGCCGA AAGGCUGC	55	UAACUCAGAGAACUUG UCCUGG	56

25	UGCCUGAGACCUCA AUACCAGCAGCCGA AAGGCUGC	57	UGGUAUUGAGGUCUCA GGCAGG	58
26	CCCCAAGUCCACCU GCCUAAGCAGCCGA AAGGCUGC	59	UUAGGCAGGUGGACUU GGGGGG	60
27	CCCAAGUCCACCUG CCUAUAGCAGCCGA AAGGCUGC	61	UAUAGGCAGGUGGACU UGGGGG	62
28	CAAGUCCACCUGCC UAUCCAGCAGCCGA AAGGCUGC	63	UGGAUAGGCAGGUGGA CUUGGG	64
29	AAGUCCACCUGCCU AUCCAAGCAGCCGA AAGGCUGC	65	UUGGAUAGGCAGGUGG ACUUGG	66
30	AGUCCACCUGCCUA UCCAUAAGCAGCCGA AAGGCUGC	67	UAUGGAUAGGCAGGUG GACUGG	68
31	GUCCACCUGCCUAU CCAUCAGCAGCCGA AAGGCUGC	69	UGAUGGAUAGGCAGGU GGACGG	70
32	UCCACCUGCCUAUC CAUCCAGCAGCCGA AAGGCUGC	71	UGGAUGGAUAGGCAGG UGGAGG	72
33	CCACCUGCCUAUCC AUCCUAGCAGCCGA AAGGCUGC	73	UAGGAUGGAUAGGCAG GUGGGG	74
34	CACCUGCCUAUCCA UCCUGAGCAGCCGA AAGGCUGC	75	UCAGGAUGGAUAGGCA GGUGGG	76
35	CCUGCCUAUCCAUC CUGCGAGCAGCCGA AAGGCUGC	77	UCGCAGGAUGGAUAGG CAGGGG	78
36	UCCAUCCUGCGAGC UCCUAGCAGCCGA AAGGCUGC	79	UAAGGAGCUCGCAGGA UGGAGG	80
37	CAUCCUGCGAGCUC CUUGGAGCAGCCGA AAGGCUGC	81	UCCAAGGAGCUCGCAG GAUGGG	82
38	AUCCUGCGAGCUCC UUGGGAGCAGCCGA AAGGCUGC	83	UCCCAAGGAGCUCGCA GGAUGG	84
39	UCCUGCGAGCUCCU UGGGUAGCAGCCGA AAGGCUGC	85	UACCCAAGGAGCUCGC AGGAGG	86
40	GCUGCCCCUGUAGG UUGCUAGCAGCCGA AAGGCUGC	87	UAGCAACCUACAGGGG CAGCGG	88

41	GUAGGUUGCUUAA AAGGGAAGCAGCCG AAAGGCUGC	89	UUCCCUUUUAAGCAAC CUACGG	90
42	UAGGUUGCUUAAA AGGGACAGCAGCCG AAAGGCUGC	91	UGUCCCUUUUAAGCAA CCUAGG	92
43	UUGCUUAAAAGGG ACAGUAAGCAGCCG AAAGGCUGC	93	UUACUGUCCCUUUUAA GCAAGG	94
44	UGCUUAAAAGGGAC AGUAUAGCAGCCGA AAGGCUGC	95	UAUACUGUCCCUUUUA AGCAGG	96
45	GCUUAAAAGGGACA GUUUUAGCAGCCGA AAGGCUGC	97	UAAUACUGUCCCUUUU AAGCGG	98
46	CUUAAAAGGGACAG UAUUCAGCAGCCGA AAGGCUGC	99	UGAAUACUGUCCCUUU UAAGGG	100
47	AAAAGGGACAGUA UUCUCAAGCAGCCG AAAGGCUGC	101	UUGAGAAUACUGUCCC UUUUGG	102
48	GGACAGUAUUCUCA GUGCUAGCAGCCGA AAGGCUGC	103	UAGCACUGAGAAUACU GUCCGG	104
49	GACAGUAUUCUCAG UGCUCAGCAGCCGA AAGGCUGC	105	UGAGCACUGAGAAUAC UGUCGG	106
50	CAGUAUUCUCAGUG CUCUCAGCAGCCGA AAGGCUGC	107	UGAGAGCACUGAGAAU ACUGGG	108
51	UAAAGCUGGACAAG AAGCUAGCAGCCGA AAGGCUGC	109	UAGCUUCUUGUCCAGC UUUAGG	110
52	AAAGCUGGACAAGA AGCUGAGCAGCCGA AAGGCUGC	111	UCAGCUUCUUGUCCAG CUUUGG	112
53	CUGUCCCUAAUAAA GCUGGAGCAGCCGA AAGGCUGC	113	UCCAGCUUUUUUAGGG ACAGGG	114
54	AGCUUCAUGCAGGG UUACAAGCAGCCGA AAGGCUGC	115	UUGUAACCCUGCAUGA AGCUGG	116
55	CUGGAGCACCGUUA AGGACAGCAGCCGA AAGGCUGC	117	UGUCCUUAACGGUGCU CCAGGG	118
56	GCACCGUUAAGGAC AAGUUAGCAGCCGA AAGGCUGC	119	UAACUUGUCCUUAACG GUGCGG	120

57	UGUAGGUUGCUUA AAAGGGAGCAGCCG AAAGGCUGC	121	UCCCUUUUAAGCAACC UACAGG	122
58	GUUGCUUAAAAGG GACAGUAGCAGCCG AAAGGCUGC	123	UACUGUCCCUUUUAAG CAACGG	124
59	GAGACCGUUAAGG ACAAGAGCAGCCGA AAGGCUGC	125	UCUUGUCCUUAACGGU GCUCGG	126
60	AGCACCGUUAAGGA CAAGUAGCAGCCGA AAGGCUGC	127	UACUUGUCCUUAACGG UGCUGG	128
61	CUGUAGGUUGCUUA AAAGGAGCAGCCGA AAGGCUGC	129	UCCUUUUUAAGCAACCU ACAGGG	130
62	AGGUUGCUUAAAA GGGACAAGCAGCCG AAAGGCUGC	131	UUGUCCCUUUUAAGCA ACCUGG	132
63	GGUUGCUUAAAAG GGACAGAGCAGCCG AAAGGCUGC	133	UCUGUCCCUUUUAAGC AACCGG	134
64	CCAAUAAAAGCUGGA CAAGAAGCAGCCGA AAGGCUGC	135	UUCUUGUCCAGCUUUA UUGGGG	136
65	AUGGCUUCAGUUC CUGAAAGCAGCCGA AAGGCUGC	137	UUUCAGGGAACUGAAG CCAUGG	138
66	GCUUCAGUUCCUG AAAGAAGCAGCCGA AAGGCUGC	139	UUCUUUCAGGGAACUG AAGCGG	140
67	CAGUUCCCUGAAAG ACUACAGCAGCCGA AAGGCUGC	141	UGUAGUCUUUCAGGGA ACUGGG	142
68	AGUUCCCUGAAAGA CUACUAGCAGCCGA AAGGCUGC	143	UAGUAGUCUUUCAGGG AACUGG	144
69	CCUGAAAGACUACU GGAGCAGCAGCCGA AAGGCUGC	145	UGCUCAGUAGUCUUU CAGGGG	146
70	GAAAGACUACUGGA GCACCAGCAGCCGA AAGGCUGC	147	UGGUGCUCCAGUAGUC UUUCGG	148
71	GACUACUGGAGCAC CGUUAAGCAGCCGA AAGGCUGC	149	UUAACGGUGCUCCAGU AGUCGG	150
72	ACUGGAGCACCGUU AAGGAAGCAGCCGA AAGGCUGC	151	UUCCUUAACGGUGCUC CAGUGG	152

73	GGAGCACCGUUAAG GACAAAGCAGCCGA AAGGCUGC	153	UUUGUCCUUAACGGUG CUCCGG	154
74	GCUUCAUGCAGGGU UACAUAGCAGCCGA AAGGCUGC	155	UAUGUAACCCUGCAUG AAGCGG	156
75	CACCGUUAAGGACA AGUUCAGCAGCCGA AAGGCUGC	157	UGAACUUGUCCUUAAC GGUGGG	158
76	ACAAGUUCUCUGAG UUCUGAGCAGCCGA AAGGCUGC	159	UCAGAACUCAGAGAAC UUGUGG	160
77	AAGUUCUCUGAGUU CUGGGAGCAGCCGA AAGGCUGC	161	UCCCAGAACUCAGAGA ACUUGG	162
78	AGUUCUCUGAGUUC UGGGAAGCAGCCGA AAGGCUGC	163	UUCCCAGAACUCAGAG AACUGG	164
79	GUUCUCUGAGUUCU GGGAUAGCAGCCGA AAGGCUGC	165	UAUCCCAGAACUCAGA GAACGG	166
80	GGACCCUGAGGUCA GACCAAGCAGCCGA AAGGCUGC	167	UUGGUCUGACCUCAGG GUCCGG	168
81	GUAUUCUCAGUGCU CUCCUAGCAGCCGA AAGGCUGC	169	UAGGAGAGCACUGAGA AUACGG	170

[00233] Table 3: GalXC-APOC3 Oligonucleotides (modified).

GalXC-APOC3	Sense Strand (passenger; 36-mer)	SEQ ID NO:	Antisense Strand (guide; 22-mer)	SEQ ID NO:
1	[mCs][mU][mA][mG][mA][mG][mG][fC][fA][fG][fC][mU][mG][mC][mU][mC][mC][mA][m G][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	171	[MePhosphonate-4O- mUs][fCs][fUs][fG][fG][mA][fG][mC][mA][fG][mC][m U][mG][fC][mC][mU][mC][mU][mA][mGs][mGs][mG]	172
2	[mGs][mG][mU][mA][mC][mU][mC][fC][fU][fU][fG][mU][mU][mG][mU][mU][mG][mC][m C][mA][mG][mC][mA][mG][mC][mC][mG][ade	173	[MePhosphonate-4O- mUs][fGs][fGs][fC][fA][mA][fC][mA][mA][fC][mA][m A][mG][fG][mA][mG][mU][mA][mC][mCs][mGs][mG]	174

	mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]			
3	[mGs][mA][mG][mG][mC][mC][mG][fA][fG][fG][fA][mU][mG][mC][mC][mU][mC][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	175	[MePhosphonate-4O-mUs][fGs][fGs][fC][fA][mA][fC][mA][fC][mA][mA][mG][fG][mA][mG][mU][mA][mC][mCs][mGs][mG]	176
4	[mCs][mC][mU][mU][mC][mU][mC][fA][fG][fC][fU][mU][mC][mA][mU][mG][mC][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	177	[MePhosphonate-4O-mUs][fCs][fUs][fG][fC][mA][fU][mG][mA][fA][mG][mC][mU][fG][mA][mG][mA][mA][mG][mGs][mGs][mG]	178
5	[mCs][mU][mU][mC][mU][mC][mA][fG][fC][fU][fU][mC][mA][mU][mG][mC][mA][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	179	[MePhosphonate-4O-mUs][fCs][fCs][fU][fG][mC][fA][mU][mG][fA][mA][mG][mC][fU][mG][mA][mG][mA][mA][mGs][mGs][mG]	180
6	[mCs][mU][mC][mA][mG][mC][mU][fU][fC][fA][fU][mG][mC][mA][mG][mG][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	181	[MePhosphonate-4O-mUs][fAs][fAs][fC][fC][mC][fU][mG][mC][fA][mU][mG][mA][fA][mG][mC][mU][mG][mA][mGs][mGs][mG]	182
7	[mAs][mU][mG][mC][mA][mC][mU][fG][fA][fG][fC][mA][mG][mC][mG][mU][mG][mC][mA][mA][mG][mC][mA][	183	[MePhosphonate-4O-mUs][fUs][fGs][fC][fA][mC][fG][mC][mU][fG][mC][mU][mC][fA][mG][mU][mG][mC][mA][mUs][mGs][mG]	184

	mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]			
8	[mUs][mG][mC][mA][mC][mU][mG][fA][fG][fC][fA][mG][mC][mG][mU][mG][mC][mA][m G][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	185	[MePhosphonate-4O- mUs][fCs][fUs][fG][fC][mA][fC][mG][mC][fU][mG][m C][mU][fC][mA][mG][mU][mG][mC][mAs][mGs][mG]	186
9	[mCs][mU][mG][mA][mG][mC][mA][fG][fC][fG][fU][mG][mC][mA][mG][mG][mA][mG][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	187	[MePhosphonate-4O- mUs][fAs][fCs][fU][fC][mC][fU][mG][mC][fA][mC][m G][mC][fU][mG][mC][mU][mC][mA][mGs][mGs][mG]	188
10	[mAs][mG][mC][mA][mG][mC][mG][fU][fG][fC][fA][mG][mG][mA][mG][mU][mC][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	189	[MePhosphonate-4O- mUs][fGs][fGs][fG][fA][mC][fU][mC][mC][fU][mG][m C][mA][fC][mG][mC][mU][mG][mC][mUs][mGs][mG]	190
11	[mUs][mG][mC][mA][mG][mG][mA][fG][fU][fC][fC][mC][mA][mG][mG][mU][mG][mG][m C][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	191	[MePhosphonate-4O- mUs][fGs][fCs][fC][fA][mC][fC][mU][mG][fG][mG][m A][mC][fU][mC][mC][mU][mG][mC][mAs][mGs][mG]	192
12	[mGs][mG][mG][mG][mC][mU][mG][fG][fG][fU][fG][mA][mC][mC][mG][mA][mU][mG][m	193	[MePhosphonate-4O- mUs][fCs][fCs][fA][fU][mC][fG][mG][mU][fC][mA][m	194

	G][mA][mG][mC][mA][mG][mC][mC][mC][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]		C][mC][fC][mA][mG][mC][mC][mC][mCs][mGs][mG]	
13	[mGs][mG][mC][mU][mU][mC][mA][fG][fU][fU][fC][mC][mC][mU][mG][mA][mA][mA][m G][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	195	[MePhosphonate-4O- mUs][fCs][fUs][fU][mC][fA][mG][mG][fG][mA][m A][mC][fU][mG][mA][mA][mG][mC][mCs][mGs][mG]	196
14	[mCs][mU][mU][mC][mA][mG][mU][fU][fC][fC][fC][mU][mG][mA][mA][mA][mG][mA][m C][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	197	[MePhosphonate-4O- mUs][fGs][fUs][fC][fU][mU][fU][mC][mA][fG][mG][m G][mA][fA][mC][mU][mG][mA][mA][mGs][mGs][mG]	198
15	[mUs][mU][mC][mA][mG][mU][mU][fC][fC][fC][fU][mG][mA][mA][mA][mG][mA][mC][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	199	[MePhosphonate-4O- mUs][fAs][fGs][fU][fC][mU][fU][mU][mC][fA][mG][m G][mG][fA][mA][mC][mU][mG][mA][mAs][mGs][mG]	200
16	[mAs][mG][mA][mC][mU][mA][mC][fU][fG][fG][fA][mG][mC][mA][mC][mC][mG][mU][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	201	[MePhosphonate-4O- mUs][fAs][fAs][fC][fG][mG][fU][mG][mC][fU][mC][m C][mA][fG][mU][mA][mG][mU][mC][mUs][mGs][mG]	202
17	[mUs][mA][mC][mU][mG][mG][mA][fG][fC][fA][fC][mC][mG][mU][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	203	[MePhosphonate-4O- mUs][fCs][fCs][fU][fU][mA][fA][mC][mG][fG][mU][m	204

	mU][mA][mA][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		G][mC][fU][mC][mC][mA][mG][mU][mAs][mGs][mG]	
18	[mUs][mG][mG][mA][mG][mC][mA][fC][fC][fG][fU][mU][mA][mA][mG][mG][mA][mC][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	205	[MePhosphonate-4O-mUs][fUs][fGs][fU][fC][mC][fU][mU][mA][fA][mC][mG][mG][fU][mG][mC][mU][mC][mC][mAs][mGs][mG]	206
19	[mAs][mC][mC][mG][mU][mU][mA][fA][fG][fG][fA][mC][mA][mA][mG][mU][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	207	[MePhosphonate-4O-mUs][fAs][fGs][fA][fA][mC][fU][mU][mG][fU][mC][mC][mU][fU][mA][mA][mC][mG][mG][mUs][mGs][mG]	208
20	[mCs][mC][mG][mU][mU][mA][mA][fG][fG][fA][fC][mA][mA][mG][mU][mU][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	209	[MePhosphonate-4O-mUs][fGs][fAs][fG][fA][mA][fC][mU][mU][fG][mU][mC][mC][fU][mU][mA][mA][mC][mG][mGs][mGs][mG]	210
21	[mCs][mG][mU][mU][mA][mA][mG][fG][fA][fC][fA][mA][mG][mU][mU][mC][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	211	[MePhosphonate-4O-mUs][fAs][fGs][fA][fG][mA][fA][mC][mU][fU][mG][mU][mC][fC][mU][mU][mA][mA][mC][mG][mGs][mGs][mG]	212
22	[mGs][mU][mU][mA][mA][mG][mG][fA][fC][fC][fA][mC][mC][mG][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	213	[MePhosphonate-4O-mUs][fCs][fAs][fG][fA][mG]	214

	fA][fA][mG][mU][mU][mC][mU][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]		][fA][mA][mC][fU][mU][mG][mU][fC][mC][mU][mU][mA][mA][mCs][mGs][mG]	
23	[mAs][mG][mG][mA][mC][mA][mA][fG][fU][fU][fC][mU][mC][mU][mG][mA][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	215	[MePhosphonate-4O-mUs][fAs][fAs][fC][fU][mC][fA][mG][mA][fG][mA][mA][mC][fU][mU][mG][mU][mC][mC][mUs][mGs][mG]	216
24	[mAs][mG][fG][mA][mC][mA][mA][fG][fU][fU][mC][fU][fC][mU][mG][mA][fG][mU][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	217	[Phosphonate-4O-mUs][fAs][fAs][mC][fU][mC][fA][fG][mA][fG][mA][fA][mC][fU][mU][fG][mU][mC][fC][mUs][mGs][mG]	218
25	[mUs][mG][mC][mC][mU][mG][mA][fG][fA][fC][fC][mU][mC][mA][mA][mU][mA][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	219	[MePhosphonate-4O-mUs][fGs][fGs][fU][fA][mU][fU][mG][mA][fG][mG][mU][mC][fU][mC][mA][mG][mG][mC][mAs][mGs][mG]	220
26	[mCs][mC][mC][mC][mA][mA][mG][fU][fC][fC][fA][mC][mC][mU][mG][mC][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	221	[MePhosphonate-4O-mUs][fUs][fAs][fG][fG][mC][fA][mG][mG][fU][mG][mG][mA][fC][mU][mU][mG][mG][mG][mGs][mGs][mG]	222

27	[mCs][mC][mC][mA][m A][mG][mU][fC][fC][f A][fC][mC][mU][mG][mC][mC][mU][mA][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	223	[MePhosphonate-4O- mUs][fAs][fUs][fA][fG][mG][fC][mA][mG][fG][mU][m G][mG][fA][mC][mU][mU][mG][mG][mGs][mGs][mG]	224
28	[mCs][mA][mA][mG][mU][mC][mC][fA][fC][fC][fU][mG][mC][mC][mU][mA][mU][mC][m C][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	225	[MePhosphonate-4O- mUs][fGs][fGs][fA][fU][mA][fG][mG][mC][fA][mG][m G][mU][fG][mG][mA][mC][mU][mU][mGs][mGs][mG]	226
29	[mAs][mA][mG][mU][mC][mC][mA][fC][fC][fU][fG][mC][mC][mU][mA][mU][mC][mC][m A][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	227	[MePhosphonate-4O- mUs][fUs][fGs][fG][fA][mU][fA][mG][mG][fC][mA][m G][mG][fU][mG][mG][mA][mC][mU][mUs][mGs][mG]	228
30	[mAs][mG][mU][mC][mC][mA][mC][fC][fU][fG][fC][mC][mU][mA][mU][mC][mC][mA][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	229	[MePhosphonate-4O- mUs][fAs][fUs][fG][fG][mA][fU][mA][mG][fG][mC][m A][mG][fG][mU][mG][mG][mA][mC][mUs][mGs][mG]	230
31	[mGs][mU][mC][mC][mA][mC][mC][fU][fG][fC][fC][mU][mA][mU][mC][mC][mA][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA-	231	[MePhosphonate-4O- mUs][fGs][fAs][fU][fG][mG][fA][mU][mA][fG][mG][m C][mA][fG][mG][mU][mG][mG][mA][mCs][mGs][mG]	232

	GalNAc][mG][mG][mC][mU][mG][mC]			
32	[mUs][mC][mC][mA][mC][mC][mU][fG][fC][fC][fU][mA][mU][mC][mC][mA][mU][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	233	[MePhosphonate-4O-mUs][fGs][fGs][fA][fU][mG][fG][mA][mU][fA][mG][mG][mC][fA][mG][mG][mU][mG][mG][mAs][mGs][mG]	234
33	[mCs][mC][mA][mC][mC][mU][mG][fC][fC][fU][fA][mU][mC][mC][mA][mU][mC][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	235	[MePhosphonate-4O-mUs][fAs][fGs][fG][fA][mU][fG][mG][mA][fU][mA][mG][mG][fC][mA][mG][mG][mU][mG][mGs][mGs][mG]	236
34	[mCs][mA][mC][mC][mU][mG][mC][fC][fU][fA][fU][mC][mC][mA][mU][mC][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	237	[MePhosphonate-4O-mUs][fCs][fAs][fG][fG][mA][fU][mG][mG][fA][mU][mA][mG][fG][mC][mA][mG][mG][mU][mGs][mGs][mG]	238
35	[mCs][mC][mU][mG][mC][mC][mU][fA][fU][fC][fC][mA][mU][mC][mC][mU][mG][mC][mC][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	239	[MePhosphonate-4O-mUs][fCs][fGs][fC][fA][mG][fG][mA][mU][fG][mG][mA][mU][fA][mG][mG][mC][mA][mG][mGs][mGs][mG]	240
36	[mUs][mC][mC][mA][mU][mC][mC][fU][fG][fC][fG][mA][mG][mC][mU][mC][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-	241	[MePhosphonate-4O-mUs][fAs][fAs][fG][fG][mA][fG][mC][mU][fC][mG][mC][mA][fG][mG][mA][mU][mG][mG][mAs][mGs][mG]	242

	GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]			
37	[mCs][mA][mU][mC][mC][mU][mG][fC][fG][fA][fG][mC][mU][mC][mC][mU][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]	243	[MePhosphonate-4O-mUs][fCs][fCs][fA][fA][mG][fG][mA][mG][fC][mU][mC][mG][fC][mA][mG][mG][mA][mU][mGs][mGs][mG]	244
38	[mAs][mU][mC][mC][mU][mG][mC][fG][fA][fG][fC][mU][mC][mC][mU][mU][mG][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]	245	[MePhosphonate-4O-mUs][fCs][fCs][fC][fA][mA][fG][mG][mA][fG][mC][mU][mC][fG][mC][mA][mG][mG][mA][mUs][mGs][mG]	246
39	[mUs][mC][mC][mU][mG][mC][mG][fA][fG][fC][fU][mC][mC][mU][mU][mG][mG][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]	247	[MePhosphonate-4O-mUs][fAs][fCs][fC][fC][mA][fA][mG][mG][fA][mG][mC][mU][fC][mG][mC][mA][mG][mG][mAs][mGs][mG]	248
40	[mGs][mC][mU][mG][mC][mC][mC][fC][fU][fG][fU][mA][mG][mG][mU][mU][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]	249	[MePhosphonate-4O-mUs][fAs][fGs][fC][fA][mA][fC][mC][mU][fA][mC][mA][mG][fG][mG][mG][mC][mA][mG][mCs][mGs][mG]	250
41	[mGs][mU][mA][mG][mG][mU][mU][fG][fC][fU][fU][mA][mA][mA][mA][mG][mG][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]	251	[MePhosphonate-4O-mUs][fUs][fCs][fC][fC][mU][fU][mU][mU][fA][mA][mG][mC][fA][mA][mC][mC][mU][mA][mCs][mGs][mG]	252

	mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]			
42	[mUs][mA][mG][mG][mU][mU][mG][fC][fU][fU][fA][mA][mA][mG][mG][mG][mA][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	253	[MePhosphonate-4O-mUs][fGs][fUs][fC][mC][fU][mU][mU][fU][mA][mA][mG][fC][mA][mA][mC][mC][mU][mAs][mGs][mG]	254
43	[mUs][mU][mG][mC][mU][mU][mA][fA][fA][fA][fG][mG][mG][mA][mC][mA][mG][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	255	[MePhosphonate-4O-mUs][fUs][fAs][fC][fU][mG][fU][mC][mC][fC][mU][mU][mU][fU][mA][mA][mG][mC][mA][mAs][mGs][mG]	256
44	[mUs][mG][mC][mU][mU][mA][mA][fA][fA][fG][fG][mG][mA][mC][mA][mG][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	257	[MePhosphonate-4O-mUs][fAs][fUs][fA][fC][mU][fG][mU][mC][fC][mC][mU][mU][fU][mU][mA][mA][mG][mC][mA][mAs][mGs][mG]	258
45	[mGs][mC][mU][mU][mA][mA][mA][fA][fG][fG][fG][mA][mC][mA][mG][mU][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	259	[MePhosphonate-4O-mUs][fAs][fAs][fU][fA][mC][fU][mG][mU][fC][mC][mC][mU][fU][mU][mU][mA][mA][mG][mCs][mGs][mG]	260
46	[mCs][mU][mU][mA][mA][mA][mA][fG][fG][fG][fA][mC][mA][mG][mU][mA][mU][mU][mC][mA][mG][mC][mA][	261	[MePhosphonate-4O-mUs][fGs][fAs][fA][fU][mA][fC][mU][mG][fU][mC][mC][mC][fU][mU][mU][mU][mA][mA][mGs][mGs][mG]	262

	mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]			
47	[mAs][mA][mA][mA][mG][mG][mG][fA][fC][fA][fG][mU][mA][mU][mU][mC][mU][mC][m A][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	263	[MePhosphonate-4O- mUs][fUs][fGs][fA][fG][mA][fA][mU][mA][fC][mU][m G][mU][fC][mC][mC][mU][mU][mU][mUs][mGs][mG]	264
48	[mGs][mG][mA][mC][mA][mG][mU][fA][fU][fU][fC][mU][mC][mA][mG][mU][mG][mC][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	265	[MePhosphonate-4O- mUs][fAs][fGs][fC][fA][mC][fU][mG][mA][fG][mA][m A][mU][fA][mC][mU][mG][mU][mC][mCs][mGs][mG]	266
49	[mGs][mA][mC][mA][mG][mU][mA][fU][fU][fC][fU][mC][mA][mG][mU][mG][mC][mU][m C][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	267	[MePhosphonate-4O- mUs][fGs][fAs][fG][fC][mA][fC][mU][mG][fA][mG][m A][mA][fU][mA][mC][mU][mG][mU][mCs][mGs][mG]	268
50	[mCs][mA][mG][mU][mA][mU][mU][fC][fU][fC][fA][mG][mU][mG][mC][mU][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	269	[MePhosphonate-4O- mUs][fGs][fAs][fG][fA][mG][fC][mA][mC][fU][mG][m A][mG][fA][mA][mU][mA][mC][mU][mGs][mGs][mG]	270
51	[mUs][mA][mA][mA][mG][mC][mU][fG][fG][fA][fC][mA][mA][mG][mA][mA][mG][mC][m	271	[MePhosphonate-4O- mUs][fAs][fGs][fC][fU][mU][fC][mU][mU][fG][mU][m	272

	U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		C][mC][fA][mG][mC][mU][mU][mU][mAs][mGs][mG]	
52	[mAs][mA][mA][mG][mC][mU][mG][fG][fA][fC][fA][mA][mG][mA][mA][mG][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	273	[MePhosphonate-4O-mUs][fCs][fAs][fG][fC][mU][fU][mC][mU][fU][mG][mU][mC][fC][mA][mG][mC][mU][mU][mUs][mGs][mG]	274
53	[mCs][mU][fG][mU][fC][mC][mC][fU][fA][fA][fU][mA][fA][mA][fG][mC][fU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	275	[MePhosphonate-4O-mUs][fCs][fCs][mA][fG][mC][fU][mU][mU][fA][mU][fU][mA][fG][mG][fG][fA][mC][fA][mGs][mGs][mG]	276
54	[mAs][mG][fC][mU][mU][mC][mA][fU][fG][fC][mA][fG][fG][mG][mU][mU][fA][mC][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	277	[Phosphonate-4O-mUs][fUs][fGs][mU][fA][mA][fC][fC][mC][fU][mG][fC][mA][fU][mG][fA][mA][mG][fC][mUs][mGs][mG]	278
55	[mCs][mU][fG][mG][mA][mG][mC][fA][fC][fC][mG][fU][fU][mA][mA][mG][fG][mA][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	279	[Phosphonate-4O-mUs][fGs][fUs][mC][fC][mU][fU][fA][mA][fC][mG][fG][mU][fG][mC][fU][mC][mC][fA][mGs][mGs][mG]	280

56	[mGs][mC][fA][mC][mC][mG][mU][fU][fA][fA][mG][fG][fA][mC][mA][mA][fG][mU][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	281	[Phosphonate-4O-mUs][fAs][fAs][mC][fU][mU][fG][fU][mC][fC][mU][fU][mA][fA][mC][fG][mG][mU][fG][mCs][mGs][mG]	282
57	[mUs][mG][fU][mA][mG][mG][mU][fU][fG][fC][mU][fU][fA][mA][mA][mA][fG][mG][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	283	[Phosphonate-4O-mUs][fCs][fCs][mC][fU][mU][fU][fU][mA][fA][mG][fC][mA][fA][mC][fC][mU][mA][fC][mAs][mGs][mG]	284
58	[mGs][mU][fU][mG][mC][mU][mU][fA][fA][fA][mA][fG][fG][mG][mA][mC][fA][mG][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	285	[Phosphonate-4O-mUs][fAs][fCs][mU][fG][mU][fC][fC][mC][fU][mU][fU][mU][fA][mA][fG][mC][mA][fA][mCs][mGs][mG]	286
59	[mGs][mA][fG][mC][fA][mC][mC][fG][fU][fU][fA][mA][fG][mG][fA][mC][fA][mA][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	287	[Phosphonate-4O-mUs][fCs][fUs][mU][fG][mU][fC][mC][mU][fU][mA][fA][mC][fG][mG][fU][fG][mC][fU][mCs][mGs][mG]	288
60	[mAs][mG][fC][mA][fC][mC][mG][fU][fU][fA][fA][mG][fG][mA][fC][mA][fA][mG][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	289	[Phosphonate-4O-mUs][fAs][fCs][mU][fU][mG][fU][mC][mC][fU][mU][fA][mA][fC][mG][fG][fU][mG][fC][mUs][mGs][mG]	290

	mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]			
61	[mCs][mU][fG][mU][fA][mG][mG][fU][fU][fG][fC][mU][fU][mA][fA][mA][fA][mG][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	291	[Phosphonate-4O-mUs][fCs][fCs][mU][fU][mU][fU][mA][mA][fG][mC][fA][mA][fC][mC][fU][fA][mC][fA][mGs][mGs][mG]	292
62	[mAs][mG][fG][mU][fU][mG][mC][fU][fU][fA][fA][mA][fA][mG][fG][fA][mA][mC][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	293	[Phosphonate-4O-mUs][fUs][fGs][mU][fC][mC][fC][mU][mU][fU][mU][fA][mA][fG][mC][fA][fA][mC][fC][mUs][mGs][mG]	294
63	[mGs][mG][fU][mU][fG][mC][mU][fU][fA][fA][fA][mA][fG][mG][fG][mA][fC][mA][mG][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	295	[Phosphonate-4O-mUs][fCs][fUs][mG][fU][mC][fC][mC][mU][fU][mU][fU][mA][fA][mG][fC][fA][mA][fC][mCs][mGs][mG]	296
64	[mCs][mC][fA][mA][fU][mA][mA][fA][fG][fC][fU][mG][fG][mA][fC][mA][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	297	[Phosphonate-4O-mUs][fUs][fCs][mU][fU][mG][fU][mC][mC][fA][mG][fC][mU][fU][mU][fA][fU][mU][fG][mGs][mGs][mG]	298

	GalNAc][mG][mG][mC][mU][mG][mC]			
65	[mAs][mU][fG][mG][fC][mU][mU][fC][fA][fG][fU][mU][fC][mC][fC][mU][fG][mA][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	299	[Phosphonate-4O-mUs][fUs][fUs][mC][fA][mG][fG][mG][mA][fA][mC][fU][mG][fA][mA][fG][fC][mC][fA][mUs][mGs][mG]	300
66	[mGs][mC][fU][mU][fC][mA][mG][fU][fU][fC][fC][mC][fU][mG][fA][mA][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	301	[Phosphonate-4O-mUs][fUs][fCs][mU][fU][mU][fC][mA][mG][fG][mG][fA][mA][fC][mU][fG][fA][mA][fG][mCs][mGs][mG]	302
67	[mCs][mA][fG][mU][fU][mC][mC][fC][fU][fG][fA][mA][fA][mG][fA][mC][fU][mA][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	303	[Phosphonate-4O-mUs][fGs][fUs][mA][fG][mU][fC][mU][mU][fU][mC][fA][mG][fG][mG][fA][fA][mC][fU][mGs][mGs][mG]	304
68	[mAs][mG][fU][mU][fC][mC][mC][fU][fG][fA][fA][mA][fG][mA][fC][mU][fA][mC][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	305	[Phosphonate-4O-mUs][fAs][fGs][mU][fA][mG][fU][mC][mU][fU][mU][fC][mA][fG][mG][fG][fA][mA][fC][mUs][mGs][mG]	306
69	[mCs][mC][fU][mG][fA][mA][mA][fG][fA][fC][fU][mA][fC][mU][fG][fU][mU][mG][mC]	307	[Phosphonate-4O-mUs][fGs][fCs][mU][fC][mC][fA][mG][mU][fA][mG][fU][mU][mG][mC]	308

	mG][fA][mG][mC][mA] [mG][mC][mA][mG][m C][mC][prgG-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][mG][mG][mC][mU][mG][mC]		U][mC][fU][mU][fU][fC][m A][fG][mGs][mGs][mG]	
70	[mGs][mA][fA][mA][fG][mA][mC][fU][fA][fC] [fU][mG][fG][mA][fG][mC][fA][mC][mC][mA] [mG][mC][mA][mG][m C][mC][prgG-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][mG][mG][mC][mU][mG][mC]	309	[Phosphonate-4O- mUs][fGs][fGs][mU][fG][m C][fU][mC][mC][fA][mG][f U][mA][fG][mU][fC][fU][m U][fU][mCs][mGs][mG]	310
71	[mGs][mA][fC][mU][fA][mC][mU][fG][fG][fA] [fG][mC][fA][mC][fC][mG][fU][mU][mA][mA]][mG][mC][mA][mG][mC][mC][prgG-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][mG][mG][mC][mU][mG][mC]	311	[Phosphonate-4O- mUs][fUs][fAs][mA][fC][m G][fG][mU][mG][fC][mU][f C][mC][fA][mG][fU][fA][m G][fU][mCs][mGs][mG]	312
72	[mAs][mC][fU][mG][fG][mA][mG][fC][fA][fC] [fC][mG][fU][mU][fA][mA][fG][mG][mA][mA]][mG][mC][mA][mG][mC][mC][prgG-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][mG][mG][mC][mU][mG][mC]	313	[Phosphonate-4O- mUs][fUs][fCs][mC][fU][m U][fA][mA][mC][fG][mG][f U][mG][fC][mU][fC][fC][m A][fG][mUs][mGs][mG]	314
73	[mGs][mG][fA][mG][fC][mA][mC][fC][fG][fU] [fU][mA][fA][mG][fG][mA][fC][mA][mA][mA] [mG][mC][mA][mG][m C][mC][prgG-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][prgA-peg- GalNAc][mG][mG][mC][mU][mG][mC]	315	[Phosphonate-4O- mUs][fUs][fUs][mG][fU][m C][fC][mU][mU][fA][mA][f C][mG][fG][mU][fG][fC][m U][fC][mCs][mGs][mG]	316

	GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]			
74	[mGs][mC][fU][mU][fC][mA][mU][fG][fC][fA][fG][mG][fG][mU][fU][mA][fC][mA][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	317	[Phosphonate-4O-mUs][fAs][fUs][mG][fU][mA][fA][mC][mC][fC][mU][fG][mC][fA][mU][fG][fA][mA][fG][mCs][mGs][mG]	318
75	[mCs][mA][fC][mC][fG][mU][mU][fA][fA][fG][fG][mA][fC][mA][fA][mG][fU][mU][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	319	[Phosphonate-4O-mUs][fGs][fAs][mA][fC][mU][fU][mG][mU][fC][mC][fU][mU][fA][mA][fC][fG][mG][fU][mGs][mGs][mG]	320
76	[mAs][mC][fA][mA][fG][mU][mU][fC][fU][fC][fU][mG][fA][mG][fU][mU][fC][mU][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	321	[Phosphonate-4O-mUs][fCs][fAs][mG][fA][mA][fC][mU][mC][fA][mG][fA][mG][fA][mA][fC][fU][mU][fG][mUs][mGs][mG]	322
77	[mAs][mA][fG][mU][mU][mC][mU][fC][fU][fG][mA][fG][fU][mU][mC][mU][fG][mG][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	323	[Phosphonate-4O-mUs][fCs][fCs][mC][fA][mG][fA][fA][mC][fU][mC][fA][mG][fA][mG][fA][mA][mC][fU][mUs][mGs][mG]	324
78	[mAs][mG][fU][mU][mC][mU][mC][fU][fG][f	325	[Phosphonate-4O-mUs][fUs][fCs][mC][fC][m	326

	A][mG][fU][fU][mC][mU][mG][fG][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]		A][fG][fA][mA][fC][mU][fC][mA][fG][mA][fG][mA][mA][fC][mUs][mGs][mG]	
79	[mGs][mU][fU][mC][mU][mC][mU][fG][fA][fG][mU][fU][fC][mU][mG][mG][fG][mA][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	327	[Phosphonate-4O-mUs][fAs][fUs][mC][fC][mC][fA][fG][mA][fA][mC][fU][mC][fA][mG][fA][mG][mA][fA][mCs][mGs][mG]	328
80	[mGs][mG][fA][mC][mC][mC][mU][fG][fA][fG][mG][fU][fC][mA][mG][mA][fC][mC][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	329	[Phosphonate-4O-mUs][fUs][fGs][mG][fU][mC][fU][fG][mA][fC][mC][fU][mC][fA][mG][fG][mG][mU][fC][mCs][mGs][mG]	330
81	[mGs][mU][fA][mU][mU][mC][mU][fC][fA][fG][mU][fG][fC][mU][mC][mU][fC][mC][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	331	[Phosphonate-4O-mUs][fAs][fGs][mG][fA][mG][fA][fG][mC][fA][mC][fU][mG][fA][mG][fA][mA][mU][fA][mCs][mGs][mG]	332

IN VIVO FUNCTION

[00234] Example 4: RNAi Oligonucleotide Inhibition of *APOC3* Expression *In Vitro*

[00235] *Mouse studies:* Various GalXC APOC3 oligonucleotides, which are listed in Tables 2 (unmodified) and 3 (modified), are evaluated in hydrodynamic injection (HDI) mouse model.

Additional HDI studies are listed in Tables 5-13. For these HDI studies, the mice are engineered to transiently express human APOC3 mRNA in hepatocytes. A GalXC APOC3 oligonucleotide control is used as a benchmark control. Briefly, 6-8-week-old female CD-1 mice are treated SQ with a GalXC APOC3 oligonucleotide at a dose level of 1 mg/kg. Three days later (72 hr), the mice are hydrodynamically injected with a DNA plasmid encoding the full human *APOC3* gene under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after introduction of the plasmid, liver samples are collected. Total RNA derived from these mice are individualized to qRT-PCR analysis for APOC3 mRNA, relative to mice treated only with an identical volume of PBS. The values are normalized for transfection efficiency using the NeoR gene included on the plasmid.

[00236] As shown in Tables 4-12, a number of GalXC APOC3 oligonucleotides tested inhibited APOC3 expression, as determined by a reduced amount of APOC3 mRNA in liver samples from oligonucleotide-treated mice relative to mice treated with PBS. The mean % of remaining APOC3 mRNA in liver samples of mice treated with the benchmark GalXC APOC3 oligonucleotide control relative to mice treated with PBS. Table 4 shows that several the 12 GalXC APOC3 oligonucleotides tested inhibit APOC3 expression to a greater extent than the reference GalXC APOC3 oligonucleotide used as control. Sequences of these oligonucleotides along with the modification patterns and SEQ ID NOs. are disclosed in Tables 2 and 3 in connection with FIG. 1.

[00237] Table 4: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 3 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal						
	1	2	3	4	5	Average	SEM
PBS	58.2	49.5	117.8	174.5	--	100.0	29.1
6	40.8	21.4	26.1	21.5	35.8	30.9	4.9
15	17.7	31.1	21.5	14.4	4.3	17.8	4.4
20	15.8	20.1	22.0	7.3	10.5	15.2	2.8
22	27.0	17.9	27.0	39.7	20.2	26.4	3.8
41	35.4	42.5	30.8	11.9	7.1	25.5	6.9
42	17.1	39.7	52.2	24.1	15.2	29.7	7.1
43	58.1	53.9	129.4	117.7	60.7	84.0	16.3
54	71.4	77.4	35.1	60.8	35.8	56.1	8.9
55	116.9	73.4	90.0	68.4	80.7	85.9	8.6
56	34.3	32.4	16.3	74.9	--	39.5	12.5
57	77.3	111.4	45.2	52.4	71.5	71.5	11.6
58	--	49.8	7.6	24.4	75.8	49.4	10.5

[00238] Tables 5-12 show additional sets of HDI mouse studies with GalXC-APOC3 oligonucleotides using the same reference oligonucleotide.

[00239] Table 5: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 3 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal					Average	SEM
	1	2	3	4	5		
PBS	126.6	158.2	50.1	107.6	57.5	100.0	20.6
13	45.7	29.7	23.7	18.6	34.9	30.5	4.7
14	35.2	14.9	25.7	30.5	21.7	25.6	3.5
15	4.4	6.3	11.3	--	--	7.3	2.0
17	22.2	29.4	21.7	18.4	15.6	21.4	2.3
18	17.1	35.8	25.4	24.6	32.69	27.1	3.3
44	12.2	23.1	7.4	12.0	10.9	13.1	2.6
59	52.5	53.1	56.0	38.2	38.8	47.7	3.8
60	36.4	58.9	45.1	31.2	39.4	42.2	4.7
61	25.7	36.1	98.2	51.9	102.7	62.9	15.9
62	73.7	56.3	76.5	41.8	121.6	74.0	13.5
63	136.5	75.2	42.1	116.6	31.9	80.4	20.4
64	54.6	48.6	37.6	48.5	62.8	50.4	4.1

[00240] Table 6: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 3 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal					Average	SEM
	1	2	3	4	5		
PBS	90.2	130.2	60.7	75.3	143.6	100.0	15.9
15	18.3	36.6	22.0	21.3	21.9	24.0	3.2
44	18.9	29.2	15.6	18.2	18.6	20.1	2.3
45	29.4	26.1	41.3	25.4	27.0	29.8	2.9
46	25.4	18.6	30.5	26.0	13.5	22.8	3.0
65	54.5	57.3	80.7	75.5	57.6	65.1	5.4
66	42.8	72.7	30.8	35.8	54.3	47.3	7.5
67	44.3	54.4	32.4	44.8	38.4	42.9	3.7
68	36.6	33.8	46.6	35.7	48.0	40.1	3.0
69	40.3	48.2	26.9	31.5	46.5	38.7	4.1
70	128.1	24.3	29.8	70.5	55.7	61.7	18.6
71	72.1	74.7	65.0	83.2	54.0	69.8	4.9
72	66.0	39.9	51.7	38.3	38.8	47.0	5.4
73	53.8	41.2	37.9	42.6	74.8	50.0	6.7

[00241] Table 7: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 3 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice; Assay 1 top table, and Assay 2 bottom table).

GalXC-APOC3	Assay 1						
	Animal						SEM
	1	2	3	4	5	Average	
PBS	103.4	91.8	76.1	133.6	95.1	100.0	9.5
15	47.5	38.6	24.6	23.9	40.1	34.9	4.6
19	64.1	24.0	25.5	22.4	33.3	33.8	7.8
21	20.9	39.1	22.5	18.5	--	25.2	4.7
23	16.8	13.2	30.7	20.1	15.0	19.2	3.1
51	53.9	25.2	25.4	24.4	54.4	36.7	7.1
74	59.5	73.2	101.2	63.2	67.0	72.8	7.5
75	79.9	75.9	83.6	106.3	124.1	93.9	9.2
76	69.1	38.9	60.6	49.9	59.5	55.6	5.2
77	55.0	44.8	72.8	89.9	93.5	71.2	9.5
78	76.8	65.3	84.5	79.9	98.3	81.0	5.4
79	68.7	62.0	83.9	63.9	98.2	75.3	6.9
80	75.2	97.6	102.2	68.6	91.4	87.0	6.5
81	55.6	36.3	55.4	44.4	58.8	50.1	4.2

GalXC-APOC3	Assay 2						
	Animal						SEM
	1	2	3	4	5	Average	
PBS	111.7	78.9	77.3	131.9	100.3	100.0	10.3
15	57.1	42.3	34.1	27.4	47.6	41.7	5.2
19	91.7	60.2	64.8	71.6	67.2	71.1	5.5
21	24.6	51.4	25.7	21.7	--	30.9	6.9
23	23.5	20.6	34.4	31.7	24.5	26.9	2.6
51	57.9	33.8	32.9	30.7	43.5	39.8	5.0
74	66.1	72.3	87.2	60.1	59.7	69.1	5.1
75	91.4	82.9	133.6	109.6	124.4	108.4	9.6
76	74.0	51.0	75.9	53.4	59.6	62.8	5.2
77	45.4	52.1	81.5	77.5	116.7	74.6	12.6
78	69.4	60.1	82.7	93.8	89.3	79.1	6.3
79	79.1	71.4	79.8	77.5	106.3	82.8	6.1
80	115.2	164.4	121.3	109.9	191.2	140.4	15.9
81	63.2	42.9	57.6	48.2	62.4	54.8	4.0

[00242] Table 8: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 1 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

	Animal
--	--------

GalXC-APOC3	1	2	3	4	5	Average	SEM
PBS	112.0	119.2	92.8	76.9	--	100.0	9.7
6	15.4	71.6	23.4	34.9	41.1	37.3	9.6
13	82.7	150.1	88.9	86.4	122.1	106.0	13.1
14	28.8	33.6	33.1	37.3	57.0	38.0	4.9
15	21.4	15.2	23.6	19.7	18.4	19.6	1.4
17	39.4	53.7	32.5	58.6	49.5	46.8	4.8
18	22.5	34.6	27.4	15.9	21.8	24.4	3.1
19	13.9	24.6	33.8	13.8	16.5	20.5	3.9
20	83.8	28.0	34.5	66.8	43.1	51.2	10.5
21	42.8	18.7	105.3	26.1	25.7	43.7	15.9
22	39.5	44.9	69.1	36.1	--	47.4	7.5
23	43.6	39.9	75.1	33.5	20.1	42.4	9.1
41	48.4	30.9	16.1	35.3	19.3	30.0	5.8
42	76.3	59.1	79.1	50.1	78.4	68.6	5.9
44	122.3	46.4	39.7	40.5	34.8	56.7	16.5
45	35.7	30.5	45.9	90.2	--	50.6	13.6
46	12.4	8.3	25.0	5.8	58.0	21.9	9.6
51	43.6	82.4	81.3	113.3	74.9	79.1	11.1

[00243] Table 9: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 1 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal						Average	SEM
	1	2	3	4	5			
PBS	98.5	72.7	130.1	93.0	105.8		100.0	9.3
1	123.9	61.4	118.7	114.8	81.3		100.0	12.2
6	58.5	78.2	76.4	41.6	26.0		56.1	10.0
14	74.8	161.2	100.1	75.8	139.9		110.4	17.4
15	82.7	67.4	67.5	62.5	51.6		66.3	5.0
16	118.0	77.4	85.2	178.4	117.2		115.3	17.8
18	90.7	51.3	87.6	93.6	97.8		84.2	8.4
19	52.9	34.0	72.8	68.2	75.5		60.7	7.7
21	119.6	93.2	110.5	57.4	80.2		92.2	11.0
25	141.0	68.7	69.6	66.6	85.0		86.2	14.1
40	65.9	55.4	53.1	128.7	80.5		76.7	13.9
41	57.4	173.7	41.8	61.5	44.8		75.9	24.7
43	87.9	39.4	81.4	54.0	81.5		68.8	9.4
46	45.5	43.8	32.2	35.4	65.8		44.6	5.9
47	35.5	58.5	24.4	34.5	19.4		34.5	6.7
52	132.4	61.3	124.5	57.0	122.5		99.6	16.6

[00244] Table 10: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 1 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal						Average	SEM
	1	2	3	4	5			
PBS	89.5	82.7	158.9	72.2	96.6	100.0	15.3	
2	126.1	88.2	--	95.6	77.0	96.7	10.5	
3	84.6	87.3	56.7	93.8	68.0	77.4	6.6	
4	107.0	--	108.8	81.3	79.4	94.1	8.0	
5	71.5	102.7	95.2	97.7	531	84.0	9.4	
7	75.5	69.9	128.7	82.1	127.5	96.7	13.0	
8	87.4	106.1	125.3	119.2	110.4	109.7	6.5	
9	63.8	65.2	58.4	54.2	55.1	59.3	2.2	
10	81.5	151.4	65.0	60.3	94.3	90.5	16.4	
11	88.7	106.3	80.4	88.4	91.1	91.0	4.2	
12	96.4	78.0	99.4	69.8	82.6	85.3	5.6	
15	33.4	25.8	45.8	52.9	50.5	41.7	5.2	
26	52.0	87.1	62.9	53.1	47.8	60.6	7.1	
27	84.8	76.5	80.2	45.4	78.8	73.1	7.1	
28	82.3	111.2	74.2	80.7	64.8	82.6	7.8	
29	64.4	62.5	94.5	63.4	70.2	71.0	6.0	

[00245] Table 11: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 1 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal						Average	SEM
	1	2	3	4	5			
PBS	89.5	82.7	158.9	72.2	96.6	100.0	15.3	
15	64.4	62.5	94.5	63.4	70.2	71.0	6.0	
15	33.4	25.8	45.8	52.9	50.5	41.7	5.2	
30	126.1	88.2	--	95.6	77.0	96.7	10.5	
31	84.6	83.7	56.7	93.8	68.0	77.4	6.6	
32	107.0	--	108.8	81.3	79.4	94.1	8.0	
33	71.5	102.7	95.2	97.7	53.1	84.0	9.4	
34	75.5	69.9	128.7	82.1	127.5	96.7	13.0	
35	87.4	106.1	125.3	119.2	110.4	109.7	6.5	
36	63.8	65.2	58.4	54.2	55.1	59.3	2.2	
37	81.5	151.4	65.0	60.3	94.3	90.5	16.4	
38	88.7	106.3	80.4	88.4	91.1	91.0	4.2	
39	96.4	78.0	99.4	69.8	82.6	85.3	5.6	
48	52.0	87.1	62.9	53.1	47.8	60.6	7.1	
49	84.8	76.5	80.2	45.4	78.8	73.1	7.1	
50	82.3	111.2	74.2	80.7	64.8	82.6	7.8	
50	87.5	86.6	66.8	74.0	50.0	73.0	6.9	

[00246] Table 12: 30-Day *In Vivo* Activity of Double-Common GalXC-APOC3 Oligonucleotides in Mice (GalXC single-dose, 1 mg/kg, 96-hr harvest; HDI of hAPOC3 Plasmid in Mice).

GalXC-APOC3	Animal						Average	SEM
	1	2	3	4	5			
PBS	136.0	97.0	136.9	86.2	73.6		105.9	13.0
PBS1	75.0	132.9	111.63	76.5	--		99.0	14.1
PBS2	62.8	67.4	113.4	172.8	57.9		94.9	21.9
6	84.2	96.1	52.3	63.8	82.2		73.7	6.7
9	60.0	92.3	3.6	78.4	108.7		84.6	8.0
15	35.7	62.0	80.1	71.4	48.6		59.6	7.9
19	59.5	39.9	376	66.5	43.2		49.3	5.8
26	81.3	71.7	93.0	48.5	53.0		69.5	8.4
40	86.0	62.7	36.9	85.9	74.3		69.2	9.1
41	41.1	37.1	34.0	34.5	48.8		39.1	2.7
43	62.3	87.7	89.8	82.5	83.3		81.1	4.9
46	46.7	49.7	35.0	32.2	34.9		39.7	3.5
47	34.3	52.6	71.7	24.9	38.9		44.5	8.1
49	60.5	43.2	32.1	87.5	48.9		54.4	9.5
50	62.8	67.4	113.4	172.8	57.9		94.9	21.9

[00247] Based on these results, 8 GalXC-APOC3 oligonucleotides are selected for evaluation of their ability to inhibit APOC3 expression in NHPs, 6 of which are selected for being double common and 2 of which are unique to human only. The GalXC-APOC3 oligonucleotides have chemically modified nucleotides of the pattern as shown in FIG. 1, especially FIG. 1C.

[00248] *NHP studies:* Eight GalXC-APOC3 oligonucleotides selected from the mouse studies above are evaluated in cynomolgus monkeys (*Macaca fascicularis*) for a single-dose (6 mg/kg), 84-day study. Here, the NHPs are grouped so that their mean body weights (about 5.4 kg) are comparable between the control and experimental groups. Each cohort contains 5 individuals (2 male and 3 female individuals). The GalXC-APOC3 oligonucleotides are administered SQ on Study Day 0. Blood samples are collected at 2 pre-dose time points (*i.e.*, Days -21 and 0) and then weekly after dosing for a liver enzyme panel and lipid profile. Ultrasound-guided core needle liver biopsies are collected on Study Days -21, 28, 56, and 83. At each time point, total RNA derived from the liver biopsy samples is individualized to qRT-PCR analysis to measure APOC3 mRNA in oligonucleotide-treated monkeys relative to monkeys treated with a comparable volume of PBS. To normalize the data, the measurements are made relative to the geometric mean of two reference genes, PP1B and 18S rRNA. As shown in Table 13, treating NHPs with the GalXC-APOC3 oligonucleotides inhibits *APOC3* expression in the liver, as determined by a reduced amount of APOC3 mRNA in liver samples from oligonucleotide-treated NHPs relative to NHPs treated with PBS. For all time points evaluated, GalXC-APOC3 oligonucleotides inhibit APOC3 expression to a greater extent than the benchmark PBS and time-matched controls. From the same NHP study, inhibition of

APOC3 expression is also determined by measuring APOC3 protein in serum prepared from the pre-dose and weekly blood samples by ELISA. Taken together, these results demonstrate that treating NHPs with GalXC-APOC3 oligonucleotides reduces the amount of APOC3 mRNA in the liver and concomitantly reduces the amount of APOC3 protein in the serum.

[00249] Table 13: APOC3 mRNA Knockdown of Select GalXC-APOC3 Oligonucleotides in NHP at Day 83 vs. Pre-Dose.

		Week	Animal						Avg	SEM
			1	2	3	4	5	6		
GalXC-APOC3	PBS	-3	88.8	170.9	92.7	57.8	73.8	115.9	100	16.3
		4	75.1	93.0	104.5	43.1	67.2	126	84.8	12
		8	92.2	82.7	84.2	67.5	87.5	169.9	97.3	14.9
		12	--	61.9	62.0	57.8	74.1	129.4	77	13.4
	15	-3	104.6	103.4	135.6	--	56.4	--	100	16.3
		4	16.7	25.9	16.1	--	15.8	--	18.6	2.4
		8	28.2	31.3	37.3	--	11.9	--	27.2	5.4
		12	30.6	36.0	47.4	--	11.8	--	31.5	7.4
	18	-3	89.2	69.9	106.5	104.6	129.7	--	100	9.9
		4	24.2	28.6	27.6	35.4	37.6	--	30.7	2.5
		8	21.3	35.2	36.3	22.8	33.7	--	29.9	3.2
		12	26.4	50.3	47.4	29.7	59.4	--	42.7	6.3
	19	-3	87.0	79.2	73.3	108.9	151.6	--	100	14.2
		4	83.5	45.5	45.9	46.5	71	--	58.5	7.9
		8	48.1	55.9	34.4	36.7	70.4	--	49.1	6.6
		12	--	--	--	--	--	--	--	--
	40	-3	77.2	93.0	109.5	104.4	116	--	100	6.8
		4	36.4	50.8	40.2	51.3	25.6	--	40.9	4.8
		8	35.0	38.7	36.4	37.5	26.8	--	34.9	2.1
		12	33.3	13.2	54.0	59.5	42.7	--	40.6	8.2
	41	-3	77.5	128.5	127.9	101.8	64.3	--	100	13
		4	31.6	22.9	29.1	30.7	20.3	--	26.9	2.2
		8	30.2	26.3	34.8	37.9	39.6	--	33.8	2.5
		12	23.2	35.3	36.6	42.9	45.5	--	36.7	3.9
	46	-3	69.3	93.3	99.5	119.4	118.5	--	100	9.2
		4	13.0	21.2	14.5	28.6	35.7	--	22.6	4.3
		8	22.0	58.4	29.2	17.1	98.4	--	45.0	15.2
		12	48.5	51.9	38.1	49.7	112.9	--	60.2	13.4
	47	-3	131.3	73.4	133.9	88.5	72.9	--	100.0	13.6
		4	29.2	18.1	4.9	10.3	19.8	--	16.5	4.2
		8	44.8	29.1	8.1	15.2	36	--	26.7	6.7
		12	96.1	17.7	36.7	25.5	82.7	--	51.7	15.8

		-3	139.7	85.0	69.1	91.8	114.4	--	100.0	12.3
	49	4	55.1	73.4	40.0	33.6	57.5	--	51.9	7
		8	51.6	51.4	30.2	52.0	59.0	--	48.8	4.9
		12	--	--	--	--	--	--	--	--

[00250] In addition to the above, RNA-seq of liver biopsies at Day 28 shows that GalXC-APOC3-47 is the most potent test article for knockdown of APOC3 mRNA (23.4% remaining) followed by GalXC-APOC3-46 (27.3% remaining), GalXC-15 (B, 34.4% remaining), GalXC-41 (38.4% remaining), and GalXC-18 (43.0% remaining). As shown in Table 14, GalXC-APOC3-15, GalXC-APOC3-18, GalXC-APOC3-46, and GalXC-APOC3-47 show only small overall changes in the liver transcriptome; whereas, GalXC-APOC3-41 shows changes in the expression of more genes. No GalXC guide-to-mRNA hybridization-based off-target effects except APOC3-41 are identified by this RNA-seq study.

[00251] Table 14: Percentage of APOC3 mRNA Remaining at Day 28 and Number of Differentially Expressed Genes (compared to time-matched PBS)

GalXC-APOC3	APOC3 (% remaining)	Genes With Higher Expression	Genes With Lower Expression
15	34.4	1	18
18	43	0	1
19	100.5	1	1
40	64.4	1	1
41	38.4	221	234
46	27.3	17	6
47	23.4	10	9
49	107.8	1	1

[00252] Taken together, these results show that GalXC-APOC3 oligonucleotides designed to target human APOC3 mRNA inhibit *APOC3* expression *in vivo* (as determined by the reduction of the amount of APOC3 mRNA and APOC3 protein in treated animals).

SEQUENCES

[00253] The following nucleic acid sequences and/or amino acid sequences are referred to in the disclosure and are provided below for reference.

[00254] SEQ ID NO:1 – wild-type human APOC3 (535 bp; NCBI Ref. Seq. No.

NM_000040.3)

ctgctcagttcatccctagaggcagctgctccaggaacagagtgccatgcagccccgggtactccttgtgttgccctcctggcgctc
ctggcctctgcccagcttcagaggccgaggatgcctcccttctcagcttcacgcaggggtacatgaagcacgccaccaagaccgcc
aaggatgcactgagcagcgtgcaggagtcccaggtggcccagcagggggctgggtgaccgatggcttcagttccctgaaag
actactggagcaccgttaaggacaagttctctgagttctgggatttgaccctgaggtcagaccaacttcagccgtggctgctgagac
ctcaataccccaagtcacctgcctatccatcctgcgagctcctgggtcctgcaatctccagggtgccctgtagggtgcttaaaagg
gacagtattctcagtgctctcctacccacctcatgcctggccccctccaggcatgctggcctcccaataaagctggacaagaagctg
ctatga

[00255] SEQ ID NO:2 – wild-type human APOC3 (99 aa; NCBI Ref. Seq. No.

NP_079501.2)

MQPRVLLVVALLALLASARASEAEDASLLSFMQGYMKHATKTAKDALSSVQESQV
AQQARGWVTDGFSSSLKDYWSTVKDKFSEFWDLDPVVRPTSAVAA

[00256] SEQ ID NO:3 – mouse APOC3 (631 bp; NCBI Ref. Seq. No. NM_001289755.1)

gcctgctcagttttatccctagaagcagctagctactccaggaatgccctggggaggagaggaagggaagggaagaacaagag
ctggagggagaagctctcaccaccagccatctagcccacagaaggctgggactcatggtacgtaggtgccatgcagccccggac
gtcctcactgtggccctcttggtctcctggcatctgcccagctgaagaggtagagggatcctgctgctgggctctgtacagggt
acatggaacaagcctcaagacggtccaggtatgcgctaagtagcgtgcaggagtccgatatagctgtggtggccaggggctggatg
gacaatcacttcagatccctgaaaggctactggagcaagttactgacaagttaccggcttctggattctaacctgaggaccaacc
aactccagctattgagtcgtgagacttctgtgtgcagatgtgcctgttctccatcctgctgccccctccaggcctgccaggtggccc
ctgaagggtgctttaaggggaaagtattgttctcatgtcttcacccctccctagatctcacctaacaatgctgtccctaataaagctggataa
gaagctgctgtta

[00257] SEQ ID NO:4 – mouse APOC3 (99 aa; NCBI Ref. Seq. No. NP_001276684.1)

MQPRTLTVALLALLASARAEVEGSLLLGSVQGYMEQASKTVQDALSSVQESDIA
VVARGWMDNHFRLKGYWSKFDTKFTGFWDSPEDQPTPAIES

[00258] SEQ ID NO:5 – rat APOC3 (579 bp; NCBI Ref. Seq. No. NM_001271053)

atgccctggggaggagaggaaggaggaggagacagagagaagacgctctggccactcagccagctagctacagaatgctt
ggaattcatggcctccaccctgggttctgtgtcacaggtgccatgcagccccgaatgctcctcatcgtggccctcgtgctctctg
gcctctgcccagctgatgaggagaggatcctgtgctgggctctatgcagggtacatggaacaagcctcaagacggtccag

gatgcactaagcagcatgcaggagtctgatatactgtggtggccaggggctggatggacaatcgcttcaaateccctgaaaggctact
 ggagcaagttcactgataagttcactggcctctgggagtctggcctgaggaccaactaacaacaccaactcttgagccgtgagacct
 ccatgttccagatgtgtctggccatctatcctgtgcctccgaagggtgctctaaggggaaagtatatctcatgcctttatccctccccag
 acctcacctaaacatgctgtccctaataaagctggacacgaagctgccatg

[00259] SEQ ID NO:6 – rat APOC3 (100 aa; NCBI Ref. Seq. No. NP_001257982.1)
 MQPRMLLIVALVALLASARADEGEGSLLLGSMQGYMEQASKTVQDALSSMQESDIA
 VVARGWMDNRFKSLKGYWSKFTDKFTGLWESGPEDQLTTPPLEP

[00260] SEQ ID NO:7 – primate APOC3 (567 bp; NCBI Ref. Seq. No. XM_005579730.1)
 aatataaaacaggtcagaaccctcctgcctgctctgttcacccatagaggcagctgctccaggaaacagaggcgccatgcagccc
 cgggtactcctgtgtgctgcctgctgctcactcctggcctctgccagagcttcagaggccgaggacacctccctctgtgcttcagcag
 ggctacatgcagcatgccaccaagaccgccaagatgcactgaccagcgtccaggagtcccagggtggcccagcaggccagaggc
 tgggtgaccgatggctcagttccctgaaagactactggagcacccgttaaggacaagtattctgggttctgggattgaacctgaggc
 caaaccactctggctgaggctgctgagacctcaatacccaagtcacctgcctgtccatcctgccagctccttgggtcctgcagcc
 tccagggtgctcccctgtaggttgcttaaaaggacagtattctcagtcacctcctaccgcacctcatgcctggccccctccaggcagg
 gtgtcctcccaataaagctggacaagaagctgctatga

[00261] SEQ ID NO:8 – primate APOC3 (99 aa; NCBI Ref. Seq. No. XP_005579787.1)
 MQPRVLLVAALLSLLASARASEAEDTSLLGFMQGYMQHATKTAKDALTSVQESQV
 AQQARGWVTDGFSSSLKDYWSTVKDKLSGFWDLNPEAKPTLAEEA

[00262] SEQ ID NOs:9-170: GalXC-APOC3 Oligonucleotides (unmodified)

GalXC-APOC3	Sense Strand (passenger; 36-mer)	SEQ ID NO:	Antisense Strand (guide; 22-mer)	SEQ ID NO:
1	CUAGAGGCAGCUGC UCCAGAGCAGCCGA AAGGCUGC	9	UCUGGAGCAGCUGCCU CUAGGG	10
2	GGUACUCCUUGUUG UUGCCAGCAGCCGA AAGGCUGC	11	UGGCAACAACAAGGAG UACCGG	12
3	GAGGCCGAGGAUGC CUCCAGCAGCCGA AAGGCUGC	13	UGGGAGGCAUCCUCGG CCUCGG	14
4	CCUUCUCAGCUUCA UGCAGAGCAGCCGA AAGGCUGC	15	UCUGCAUGAAGCUGAG AAGGGG	16

5	CUUCUCAGCUUCAU GCAGGAGCAGCCGA AAGGCUGC	17	UCCUGCAUGAAGCUGA GAAGGG	18
6	CUCAGCUUCAUGCA GGGUUAGCAGCCGA AAGGCUGC	19	UAACCCUGCAUGAAGC UGAGGG	20
7	AUGCACUGAGCAGC GUGCAAGCAGCCGA AAGGCUGC	21	UUGCACGCUGCUCAGU GCAUGG	22
8	UGCACUGAGCAGCG UGCAGAGCAGCCGA AAGGCUGC	23	UCUGCACGCUGCUCAG UGCAGG	24
9	CUGAGCAGCGUGCA GGAGUAGCAGCCGA AAGGCUGC	25	UACUCCUGCACGCUGC UCAGGG	26
10	AGCAGCGUGCAGGA GUCCCAGCAGCCGA AAGGCUGC	27	UGGGACUCCUGCACGC UGCUGG	28
11	UGCAGGAGUCCAG GUGGCAGCAGCCGA AAGGCUGC	29	UGCCACCUGGGACUCC UGCAGG	30
12	GGGGCUGGGUGACC GAUGGAGCAGCCGA AAGGCUGC	31	UCCAUCGGUACCCAGC CCCGG	32
13	GGCUUCAGUUCCCU GAAAGAGCAGCCGA AAGGCUGC	33	UCUUUCAGGGAACUGA AGCCGG	34
14	CUUCAGUUCCUGA AAGACAGCAGCCGA AAGGCUGC	35	UGUCUUUCAGGGAACU GAAGGG	36
15	UUCAGUUCCUGAA AGACUAGCAGCCGA AAGGCUGC	37	UAGUCUUUCAGGGAAC UGAAGG	38
16	AGACUACUGGAGCA CCGUUAGCAGCCGA AAGGCUGC	39	UAACGGUGCUCCAGUA GUCUGG	40
17	UACUGGAGCACCGU UAAGGAGCAGCCGA AAGGCUGC	41	UCCUUAACGGUGCUCC AGUAGG	42
18	UGGAGCACCGUUA GGACAAGCAGCCGA AAGGCUGC	43	UUGUCCUUAACGGUGC UCCAGG	44
19	ACCGUUAAGGACAA GUUCUAGCAGCCGA AAGGCUGC	45	UAGAACUUGUCCUUA CGGUGG	46
20	CCGUUAAGGACAAG UUCUCAGCAGCCGA AAGGCUGC	47	UGAGAACUUGUCCUUA ACGGGG	48

21	CGUUAAGGACAAGU UCUCUAGCAGCCGA AAGGCUGC	49	UAGAGAACUUGUCCUU AACGGG	50
22	GUUAAGGACAAGU UCUCUGAGCAGCCG AAAGGCUGC	51	UCAGAGAACUUGUCCU UAACGG	52
23	AGGACAAGUUCUCU GAGUUAGCAGCCGA AAGGCUGC	53	UAAUCUCAGAGAACUUG UCCUGG	54
24	AGGACAAGUUCUCU GAGUUAGCAGCCGA AAGGCUGC	55	UAAUCUCAGAGAACUUG UCCUGG	56
25	UGCCUGAGACCUCA AUACCAGCAGCCGA AAGGCUGC	57	UGGUUUUGAGGUCUCA GGCAGG	58
26	CCCCAAGUCCACCU GCCUAAGCAGCCGA AAGGCUGC	59	UUAGGCAGGUGGACUU GGGGGG	60
27	CCCAAGUCCACCU CCUAUAGCAGCCGA AAGGCUGC	61	UAUAGGCAGGUGGACU UGGGGG	62
28	CAAGUCCACCUGCC UAUCCAGCAGCCGA AAGGCUGC	63	UGGAUAGGCAGGUGGA CUUGGG	64
29	AAGUCCACCUGCCU AUCCAAGCAGCCGA AAGGCUGC	65	UUGGAUAGGCAGGUGG ACUUGG	66
30	AGUCCACCUGCCUA UCCAUAAGCAGCCGA AAGGCUGC	67	UAUGGAUAGGCAGGUG GACUGG	68
31	GUCCACCUGCCUAU CCAUCAGCAGCCGA AAGGCUGC	69	UGAUGGAUAGGCAGGU GGACGG	70
32	UCCACCUGCCUAUC CAUCCAGCAGCCGA AAGGCUGC	71	UGGAUGGAUAGGCAGG UGGAGG	72
33	CCACCUGCCUAUCC AUCCUAGCAGCCGA AAGGCUGC	73	UAGGAUGGAUAGGCAG GUGGGG	74
34	CACCUGCCUAUCCA UCCUGAGCAGCCGA AAGGCUGC	75	UCAGGAUGGAUAGGCA GGUGGG	76
35	CCUGCCUAUCCAUC CUGCGAGCAGCCGA AAGGCUGC	77	UCGCAGGAUGGAUAGG CAGGGG	78
36	UCCAUCCUGCGAGC UCCUUAGCAGCCGA AAGGCUGC	79	UAAGGAGCUCGCAGGA UGGAGG	80

37	CAUCCUGCGAGCUC CUUGGAGCAGCCGA AAGGCUGC	81	UCCAAGGAGCUCGCAG GAUGGG	82
38	AUCCUGCGAGCUCC UUGGGAGCAGCCGA AAGGCUGC	83	UCCCAAGGAGCUCGCA GGAUGG	84
39	UCCUGCGAGCUCCU UGGGUAGCAGCCGA AAGGCUGC	85	UACCCAAGGAGCUCGC AGGAGG	86
40	GCUGCCCCUGUAGG UUGCUAGCAGCCGA AAGGCUGC	87	UAGCAACCUACAGGGG CAGCGG	88
41	GUAGGUUGCUUAA AAGGGAAGCAGCCG AAAGGCUGC	89	UUCCCUUUUAAGCAAC CUACGG	90
42	UAGGUUGCUUAAA AGGGACAGCAGCCG AAAGGCUGC	91	UGUCCCUUUUAAGCAA CCUAGG	92
43	UUGCUUAAAAGGG ACAGUAAGCAGCCG AAAGGCUGC	93	UUACUGUCCCUUUUAA GCAAGG	94
44	UGCUUAAAAGGGAC AGUAUAGCAGCCGA AAGGCUGC	95	UAUACUGUCCCUUUUA AGCAGG	96
45	GCUUAAAAGGGACA GUAUUAGCAGCCGA AAGGCUGC	97	UAAUACUGUCCCUUUU AAGCGG	98
46	CUUAAAAGGGACAG UAUUCAGCAGCCGA AAGGCUGC	99	UGAAUACUGUCCCUUU UAAGGG	100
47	AAAAGGGACAGUA UUCUCAAGCAGCCG AAAGGCUGC	101	UUGAGAAUACUGUCCC UUUUGG	102
48	GGACAGUAUUCUCA GUGCUAGCAGCCGA AAGGCUGC	103	UAGCACUGAGAAUACU GUCCGG	104
49	GACAGUAUUCUCAG UGCUCAGCAGCCGA AAGGCUGC	105	UGAGCACUGAGAAUAC UGUCGG	106
50	CAGUAUUCUCAGUG CUCUCAGCAGCCGA AAGGCUGC	107	UGAGAGCACUGAGAAU ACUGGG	108
51	UAAAGCUGGACAAG AAGCUAGCAGCCGA AAGGCUGC	109	UAGCUUCUUGUCCAGC UUUAGG	110
52	AAAGCUGGACAAGA AGCUGAGCAGCCGA AAGGCUGC	111	UCAGCUUCUUGUCCAG CUUUGG	112

53	CUGUCCCUAAUAAA GCUGGAGCAGCCGA AAGGCUGC	113	UCCAGCUUUUUAUAGGG ACAGGG	114
54	AGCUUCAUGCAGGG UUACAAGCAGCCGA AAGGCUGC	115	UUGUAACCCUGCAUGA AGCUGG	116
55	CUGGAGCACCGUUA AGGACAGCAGCCGA AAGGCUGC	117	UGUCCUUAACGGUGCU CCAGGG	118
56	GCACCGUUAAGGAC AAGUUAGCAGCCGA AAGGCUGC	119	UAACUUGUCCUUAACG GUGCGG	120
57	UGUAGGUUGCUUA AAAGGGAGCAGCCG AAAGGCUGC	121	UCCCUUUUAAGCAACC UACAGG	122
58	GUUGCUUAAAAGG GACAGUAGCAGCCG AAAGGCUGC	123	UACUGUCCCUUUUAAG CAACGG	124
59	GAGCACCGUUAAGG ACAAGAGCAGCCGA AAGGCUGC	125	UCUUGUCCUUAACGGU GCUCGG	126
60	AGCACCGUUAAGGA CAAGUAGCAGCCGA AAGGCUGC	127	UACUUGUCCUUAACGG UGCUGG	128
61	CUGUAGGUUGCUUA AAAGGAGCAGCCGA AAGGCUGC	129	UCCUUUUUAAGCAACCU ACAGGG	130
62	AGGUUGCUUAAAA GGGACAAGCAGCCG AAAGGCUGC	131	UUGUCCCUUUUAAGCA ACCUGG	132
63	GGUUGCUUAAAAG GGACAGAGCAGCCG AAAGGCUGC	133	UCUGUCCCUUUUAAGC AACCGG	134
64	CCAAUAAAGCUGGA CAAGAAGCAGCCGA AAGGCUGC	135	UUCUUGUCCAGCUUUA UUGGGG	136
65	AUGGCUUCAGUUC CUGAAAGCAGCCGA AAGGCUGC	137	UUUCAGGGAACUGAAG CCAUGG	138
66	GCUUCAGUUCCUG AAAGAAGCAGCCGA AAGGCUGC	139	UUCUUUCAGGGAACUG AAGCGG	140
67	CAGUUCCUGAAAG ACUACAGCAGCCGA AAGGCUGC	141	UGUAGUCUUUCAGGGA ACUGGG	142
68	AGUUCCUGAAAGA CUACUAGCAGCCGA AAGGCUGC	143	UAGUAGUCUUUCAGGG AACUGG	144

69	CCUGAAAGACUACU GGAGCAGCAGCCGA AAGGCUGC	145	UGCUCAGUAGUCUUU CAGGGG	146
70	GAAAGACUACUGGA GCACCAGCAGCCGA AAGGCUGC	147	UGGUGCUCCAGUAGUC UUUCGG	148
71	GACUACUGGAGCAC CGUUAAGCAGCCGA AAGGCUGC	149	UUAACGGUGCUCCAGU AGUCGG	150
72	ACUGGAGCACCGUU AAGGAAGCAGCCGA AAGGCUGC	151	UUCCUUAACGGUGCUC CAGUGG	152
73	GGAGCACCGUUAAG GACAAAGCAGCCGA AAGGCUGC	153	UUUGUCCUUAACGGUG CUCCGG	154
74	GCUUCAUGCAGGGU UACAUAGCAGCCGA AAGGCUGC	155	UAUGUAACCCUGCAUG AAGCGG	156
75	CACCGUUAAGGACA AGUUCAGCAGCCGA AAGGCUGC	157	UGAACUUGUCCUUAAC GGUGGG	158
76	ACAAGUUCUCUGAG UUCUGAGCAGCCGA AAGGCUGC	159	UCAGAACUCAGAGAAC UUGUGG	160
77	AAGUUCUCUGAGUU CUGGGAGCAGCCGA AAGGCUGC	161	UCCCAGAACUCAGAGA ACUUGG	162
78	AGUUCUCUGAGUUC UGGGAAGCAGCCGA AAGGCUGC	163	UUCCCAGAACUCAGAG AACUGG	164
79	GUUCUCUGAGUUCU GGGAUAGCAGCCGA AAGGCUGC	165	UAUCCCAGAACUCAGA GAACGG	166
80	GGACCCUGAGGUCA GACCAAGCAGCCGA AAGGCUGC	167	UUGGUCUGACCUCAGG GUCCGG	168
81	GUAUUCUCAGUGCU CUCCUAGCAGCCGA AAGGCUGC	169	UAGGAGAGCACUGAGA AUACGG	170

[00263] SEQ ID NOs:171-332: GalXC-APOC3 Oligonucleotides (modified)

GalXC-APOC3	Sense Strand (passenger; 36-mer)	SEQ ID NO:	Antisense Strand (guide; 22-mer)	SEQ ID NO:
1	[mCs][mU][mA][mG][mA][mG][mG][fC][fA][fG][fC][mU][mG][mC][mU][mC][mC][mA][m	171	[MePhosphonate-4O- mUs][fCs][fUs][fG][fG][mA][fG][mC][mA][fG][mC][m	172

	G][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		U][mG][fC][mC][mU][mC][mU][mA][mGs][mGs][mG]	
2	[mGs][mG][mU][mA][mC][mU][mC][fC][fU][fU][fG][mU][mU][mG][mU][mU][mG][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	173	[MePhosphonate-4O-mUs][fGs][fGs][fC][fA][mA][fC][mA][mA][fC][mA][mA][mG][fG][mA][mG][mU][mA][mC][mCs][mGs][mG]	174
3	[mGs][mA][mG][mG][mC][mC][mG][fA][fG][fG][fA][mU][mG][mC][mC][mC][mU][mC][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	175	[MePhosphonate-4O-mUs][fGs][fGs][fC][fA][mA][fC][mA][mA][fC][mA][mA][mG][fG][mA][mG][mU][mA][mC][mCs][mGs][mG]	176
4	[mCs][mC][mU][mU][mC][mU][mC][fA][fG][fC][fU][mU][mC][mA][mU][mG][mC][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	177	[MePhosphonate-4O-mUs][fCs][fUs][fG][fC][mA][fU][mG][mA][fA][mG][mC][mU][fG][mA][mG][mA][mA][mG][mGs][mGs][mG]	178
5	[mCs][mU][mU][mC][mU][mC][mA][fG][fC][fU][fU][mC][mA][mU][mG][mC][mA][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	179	[MePhosphonate-4O-mUs][fCs][fCs][fU][fG][mC][fA][mU][mG][fA][mA][mG][mC][fU][mG][mA][mG][mA][mA][mGs][mGs][mG]	180
6	[mCs][mU][mC][mA][mG][mC][mU][fU][fC][fA][fU][mG][mC][mA][	181	[MePhosphonate-4O-mUs][fAs][fAs][fC][fC][mC][fU][mG][mC][fA][mU][m	182

	mG][mG][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		G][mA][fA][mG][mC][mU][mG][mA][mGs][mGs][mG]	
7	[mAs][mU][mG][mC][mA][mC][mU][fG][fA][fG][fC][mA][mG][mC][mG][mU][mG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	183	[MePhosphonate-4O-mUs][fUs][fGs][fC][fA][mC][fG][mC][mU][fG][mC][mU][mC][fA][mG][mU][mG][mC][mA][mUs][mGs][mG]	184
8	[mUs][mG][mC][mA][mC][mU][mG][fA][fG][fC][fA][mG][mC][mG][mU][mG][mC][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	185	[MePhosphonate-4O-mUs][fCs][fUs][fG][fC][mA][fC][mG][mC][fU][mG][mC][mU][fC][mA][mG][mU][mG][mC][mAs][mGs][mG]	186
9	[mCs][mU][mG][mA][mG][mC][mA][fG][fC][fG][fU][mG][mC][mA][mG][mG][mA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	187	[MePhosphonate-4O-mUs][fAs][fCs][fU][fC][mC][fU][mG][mC][fA][mC][mG][mC][fU][mG][mC][mU][mC][mA][mGs][mGs][mG]	188
10	[mAs][mG][mC][mA][mG][mC][mG][fU][fG][fC][fA][mG][mG][mA][mG][mU][mC][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	189	[MePhosphonate-4O-mUs][fGs][fGs][fG][fA][mC][fU][mC][mC][fU][mG][mC][mA][fC][mG][mC][mU][mG][mC][mUs][mGs][mG]	190
11	[mUs][mG][mC][mA][mG][mG][mA][fG][fU][	191	[MePhosphonate-4O-mUs][fGs][fCs][fC][fA][mC]	192

	fC][fC][mC][mA][mG][mG][mU][mG][mG][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		][fC][mU][mG][fG][mG][mA][mC][fU][mC][mC][mU][mG][mC][mAs][mGs][mG]	
12	[mGs][mG][mG][mG][mC][mU][mG][fG][fG][fU][fG][mA][mC][mC][mG][mA][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	193	[MePhosphonate-4O-mUs][fCs][fCs][fA][fU][mC][fG][mG][mU][fC][mA][mC][mC][fC][mA][mG][mC][mC][mC][mCs][mGs][mG]	194
13	[mGs][mG][mC][mU][mU][mC][mA][fG][fU][fU][fC][mC][mC][mU][mG][mA][mA][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	195	[MePhosphonate-4O-mUs][fCs][fUs][fU][fU][mC][fA][mG][mG][fG][mA][mA][mC][fU][mG][mA][mA][mG][mC][mCs][mGs][mG]	196
14	[mCs][mU][mU][mC][mA][mG][mU][fU][fC][fC][fC][mU][mG][mA][mA][mA][mG][mA][mG][mA][mC][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	197	[MePhosphonate-4O-mUs][fGs][fUs][fC][fU][mU][fU][mC][mA][fG][mG][mG][mA][fA][mC][mU][mG][mA][mA][mGs][mGs][mG]	198
15	[mUs][mU][mC][mA][mG][mU][mU][fC][fC][fC][fU][mG][mA][mA][mA][mG][mA][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	199	[MePhosphonate-4O-mUs][fAs][fGs][fU][fC][mU][fU][mU][mC][fA][mG][mG][mG][fA][mA][mC][mU][mG][mA][mAs][mGs][mG]	200

16	[mAs][mG][mA][mC][mU][mA][mC][fU][fG][fG][fA][mG][mC][mA][mC][mC][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	201	[MePhosphonate-4O-mUs][fAs][fAs][fC][fG][mG][fU][mG][mC][fU][mC][mC][mA][fG][mU][mA][mG][mU][mC][mUs][mGs][mG]	202
17	[mUs][mA][mC][mU][mG][mG][mA][fG][fC][fA][fC][mC][mG][mU][mU][mA][mA][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	203	[MePhosphonate-4O-mUs][fCs][fCs][fU][fU][mA][fA][mC][mG][fG][mU][mG][mC][fU][mC][mC][mA][mG][mU][mAs][mGs][mG]	204
18	[mUs][mG][mG][mA][mG][mC][mA][fC][fC][fG][fU][mU][mA][mA][mG][mG][mA][mC][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	205	[MePhosphonate-4O-mUs][fUs][fGs][fU][fC][mC][fU][mU][mA][fA][mC][mG][mG][fU][mG][mC][mU][mC][mC][mAs][mGs][mG]	206
19	[mAs][mC][mC][mG][mU][mU][mA][fA][fG][fG][fA][mC][mA][mA][mG][mU][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	207	[MePhosphonate-4O-mUs][fAs][fGs][fA][fA][mC][fU][mU][mG][fU][mC][mC][mU][fU][mA][mA][mC][mG][mG][mUs][mGs][mG]	208
20	[mCs][mC][mG][mU][mU][mA][mA][fG][fG][fA][fC][mA][mA][mG][mU][mU][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-	209	[MePhosphonate-4O-mUs][fGs][fAs][fG][fA][mA][fC][mU][mU][fG][mU][mC][mC][fU][mU][mA][mA][mC][mG][mGs][mGs][mG]	210

	GalNAc][mG][mG][mC][mU][mG][mC]			
21	[mCs][mG][mU][mU][mA][mA][mG][fG][fA][fC][fA][mA][mG][mU][mU][mC][mU][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	211	[MePhosphonate-4O-mUs][fAs][fGs][fA][fG][mA][fA][mC][mU][fU][mG][mU][mC][fC][mU][mU][mA][mA][mC][mGs][mGs][mG]	212
22	[mGs][mU][mU][mA][mA][mG][mG][fA][fC][fA][fA][mG][mU][mU][mC][mU][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	213	[MePhosphonate-4O-mUs][fCs][fAs][fG][fA][mG][fA][mA][mC][fU][mU][mG][mU][fC][mC][mU][mU][mA][mA][mCs][mGs][mG]	214
23	[mAs][mG][mG][mA][mC][mA][mA][fG][fU][fU][fC][mU][mC][mU][mG][mA][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	215	[MePhosphonate-4O-mUs][fAs][fAs][fC][fU][mC][fA][mG][mA][fG][mA][mA][mC][fU][mU][mG][mU][mC][mC][mUs][mGs][mG]	216
24	[mAs][mG][fG][mA][mC][mA][mA][fG][fU][fU][mC][fU][fC][mU][mG][mA][fG][mU][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	217	[Phosphonate-4O-mUs][fAs][fAs][mC][fU][mC][fA][fG][mA][fG][mA][fA][mC][fU][mU][fG][mU][mC][fC][mUs][mGs][mG]	218
25	[mUs][mG][mC][mC][mU][mG][mA][fG][fA][fC][fC][mU][mC][mA][mA][mU][mA][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade	219	[MePhosphonate-4O-mUs][fGs][fGs][fU][fA][mU][fU][mG][mA][fG][mG][mU][mC][fU][mC][mA][mG][mG][mC][mAs][mGs][mG]	220

	mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mC][mU][mG][mC]			
26	[mCs][mC][mC][mC][mA][mA][mG][fU][fC][fC][fA][mC][mC][mU][mG][mC][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	221	[MePhosphonate-4O-mUs][fUs][fAs][fG][fG][mC][fA][mG][mG][fU][mG][mG][mA][fC][mU][mU][mG][mG][mG][mGs][mGs][mG]	222
27	[mCs][mC][mC][mA][mA][mG][mU][fC][fC][fA][fC][mC][mU][mG][mC][mC][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	223	[MePhosphonate-4O-mUs][fAs][fUs][fA][fG][mG][fC][mA][mG][fG][mU][mG][mG][fA][mC][mU][mU][mG][mG][mGs][mGs][mG]	224
28	[mCs][mA][mA][mG][mU][mC][mC][fA][fC][fC][fU][mG][mC][mC][mU][mA][mU][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	225	[MePhosphonate-4O-mUs][fGs][fGs][fA][fU][mA][fG][mG][mC][fA][mG][mG][mU][fG][mG][mA][mC][mU][mU][mGs][mGs][mG]	226
29	[mAs][mA][mG][mU][mC][mC][mA][fC][fC][fU][fG][mC][mC][mU][mA][mU][mC][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	227	[MePhosphonate-4O-mUs][fUs][fGs][fG][fA][mU][fA][mG][mG][fC][mA][mG][mG][fU][mG][mG][mA][mC][mU][mUs][mGs][mG]	228
30	[mAs][mG][mU][mC][mC][mA][mC][fC][fU][fG][fC][mC][mU][mA][mU][mC][mC][mA][mU][mA][mG][mC][mA][	229	[MePhosphonate-4O-mUs][fAs][fUs][fG][fG][mA][fU][mA][mG][fG][mC][mA][mG][fG][mU][mG][mG][mA][mC][mUs][mGs][mG]	230

	mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mC][mC][mU][mG][mC]			
31	[mGs][mU][mC][mC][mA][mC][mC][fU][fG][fC][fC][mU][mA][mU][mC][mC][mA][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	231	[MePhosphonate-4O- mUs][fGs][fAs][fU][fG][mG][fA][mU][mA][fG][mG][m C][mA][fG][mG][mU][mG][mG][mA][mCs][mGs][mG]	232
32	[mUs][mC][mC][mA][mC][mC][mU][fG][fC][fC][fU][mA][mU][mC][mC][mA][mU][mC][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	233	[MePhosphonate-4O- mUs][fGs][fGs][fA][fU][mG][fG][mA][mU][fA][mG][m G][mC][fA][mG][mG][mU][mG][mG][mAs][mGs][mG]	234
33	[mCs][mC][mA][mC][m C][mU][mG][fC][fC][f U][fA][mU][mC][mC][mA][mU][mC][mC][m U][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	235	[MePhosphonate-4O- mUs][fAs][fGs][fG][fA][mU][fG][mG][mA][fU][mA][m G][mG][fC][mA][mG][mG][mU][mG][mGs][mGs][mG]	236
34	[mCs][mA][mC][mC][m U][mG][mC][fC][fU][f A][fU][mC][mC][mA][mU][mC][mC][mU][m G][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA- GalNAc][ademA- GalNAc][mG][mG][mC][mU][mG][mC]	237	[MePhosphonate-4O- mUs][fCs][fAs][fG][fG][mA][fU][mG][mG][fA][mU][m A][mG][fG][mC][mA][mG][mG][mU][mGs][mGs][mG]	238
35	[mCs][mC][mU][mG][mC][mC][mU][fA][fU][fC][fC][mA][mU][mC][mC][mU][mG][mC][m	239	[MePhosphonate-4O- mUs][fCs][fGs][fC][fA][mG][fG][mA][mU][fG][mG][m	240

	G][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		A][mU][fA][mG][mG][mC][mA][mG][mGs][mGs][mG]	
36	[mUs][mC][mC][mA][mU][mC][mC][fU][fG][fC][fG][mA][mG][mC][mU][mC][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	241	[MePhosphonate-4O-mUs][fAs][fAs][fG][fG][mA][fG][mC][mU][fC][mG][mC][mA][fG][mG][mA][mU][mG][mG][mAs][mGs][mG]	242
37	[mCs][mA][mU][mC][mC][mU][mG][fC][fG][fA][fG][mC][mU][mC][mC][mU][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	243	[MePhosphonate-4O-mUs][fCs][fCs][fA][mG][fG][mA][mG][fC][mU][mC][mG][fC][mA][mG][mG][mA][mU][mGs][mGs][mG]	244
38	[mAs][mU][mC][mC][mU][mG][mC][fG][fA][fG][fC][mU][mC][mC][mU][mU][mG][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	245	[MePhosphonate-4O-mUs][fCs][fCs][fC][fA][mA][fG][mG][mA][fG][mC][mU][mC][fG][mC][mA][mG][mG][mA][mUs][mGs][mG]	246
39	[mUs][mC][mC][mU][mG][mC][mG][fA][fG][fC][fU][mC][mC][mU][mU][mG][mG][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	247	[MePhosphonate-4O-mUs][fAs][fCs][fC][fC][mA][fA][mG][mG][fA][mG][mC][mU][fC][mG][mC][mA][mG][mG][mAs][mGs][mG]	248
40	[mGs][mC][mU][mG][mC][mC][mC][fC][fU][fG][fU][mA][mG][mG][	249	[MePhosphonate-4O-mUs][fAs][fGs][fC][fA][mA][fC][mC][mU][fA][mC][m	250

	mU][mU][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		A][mG][fG][mG][mC][mA][mG][mCs][mGs][mG]	
41	[mGs][mU][mA][mG][mG][mU][mU][fG][fC][fU][fU][mA][mA][mA][mA][mG][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	251	[MePhosphonate-4O-mUs][fUs][fCs][fC][mU][fU][mU][mU][fA][mG][mC][fA][mA][mC][mC][mU][mA][mCs][mGs][mG]	252
42	[mUs][mA][mG][mG][mU][mU][mG][fC][fU][fU][fA][mA][mA][mA][mG][mG][mG][mA][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	253	[MePhosphonate-4O-mUs][fGs][fUs][fC][fC][mC][fU][mU][mU][fU][mA][mA][mG][fC][mA][mA][mC][mC][mU][mAs][mGs][mG]	254
43	[mUs][mU][mG][mC][mU][mU][mA][fA][fA][fA][fG][mG][mG][mA][mC][mA][mG][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	255	[MePhosphonate-4O-mUs][fUs][fAs][fC][fU][mG][fU][mC][mC][fC][mU][mU][mU][fU][mA][mA][mG][mC][mA][mAs][mGs][mG]	256
44	[mUs][mG][mC][mU][mU][mA][mA][fA][fA][fG][fG][mG][mA][mC][mA][mG][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	257	[MePhosphonate-4O-mUs][fAs][fUs][fA][fC][mU][fG][mU][mC][fC][mC][mU][mU][fU][mU][mA][mA][mG][mC][mAs][mGs][mG]	258
45	[mGs][mC][mU][mU][mA][mA][mA][fA][fG][fG]	259	[MePhosphonate-4O-mUs][fAs][fAs][fU][fA][mC]	260

	fG][fG][mA][mC][mA][mG][mU][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]		][fU][mG][mU][fC][mC][mC][mU][fU][mU][mU][mA][mA][mG][mCs][mGs][mG]	
46	[mCs][mU][mU][mA][mA][mA][mA][fG][fG][fG][fA][mC][mA][mG][mU][mA][mU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	261	[MePhosphonate-4O-mUs][fGs][fAs][fA][fU][mA][fC][mU][mG][fU][mC][mC][mC][fU][mU][mU][mA][mA][mGs][mGs][mG]	262
47	[mAs][mA][mA][mA][mG][mG][mG][fA][fC][fA][fG][mU][mA][mU][mU][mC][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	263	[MePhosphonate-4O-mUs][fUs][fGs][fA][fG][mA][fA][mU][mA][fC][mU][mG][mU][fC][mC][mC][mU][mU][mU][mUs][mGs][mG]	264
48	[mGs][mG][mA][mC][mA][mG][mU][fA][fU][fU][fC][mU][mC][mA][mG][mU][mU][mG][mC][mU][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	265	[MePhosphonate-4O-mUs][fAs][fGs][fC][fA][mC][fU][mG][mA][fG][mA][mA][mU][fA][mC][mU][mG][mU][mC][mCs][mGs][mG]	266
49	[mGs][mA][mC][mA][mG][mU][mA][fU][fU][fC][fU][mC][mA][mG][mU][mG][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	267	[MePhosphonate-4O-mUs][fGs][fAs][fG][fC][mA][fC][mU][mG][fA][mG][mA][mA][fU][mA][mC][mU][mG][mU][mCs][mGs][mG]	268

50	[mCs][mA][mG][mU][mA][mU][mU][fC][fU][fC][fA][mG][mU][mG][mC][mU][mC][mU][mC][mA][mG][mC][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	269	[MePhosphonate-4O-mUs][fGs][fAs][fG][fA][mG][fC][mA][mC][fU][mG][mA][mG][fA][mA][mU][mA][mC][mU][mGs][mGs][mG]	270
51	[mUs][mA][mA][mA][mG][mC][mU][fG][fG][fA][fC][mA][mA][mG][mA][mA][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	271	[MePhosphonate-4O-mUs][fAs][fGs][fC][fU][mU][fC][mU][mU][fG][mU][mC][mC][fA][mG][mC][mU][mU][mU][mAs][mGs][mG]	272
52	[mAs][mA][mA][mG][mC][mU][mG][fG][fA][fC][fA][mA][mG][mA][mA][mG][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	273	[MePhosphonate-4O-mUs][fCs][fAs][fG][fC][mU][fU][mC][mU][fU][mG][mU][mC][fC][mA][mG][mC][mU][mU][mUs][mGs][mG]	274
53	[mCs][mU][fG][mU][fC][mC][mC][fU][fA][fA][fU][mA][fA][mA][fG][mC][fU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademaA-GalNAc][ademaA-GalNAc][ademaA-GalNAc][mG][mG][mC][mU][mG][mC]	275	[MePhosphonate-4O-mUs][fCs][fCs][mA][fG][mC][fU][mU][mU][fA][mU][fU][mA][fG][mG][fG][fA][mC][fA][mGs][mGs][mG]	276
54	[mAs][mG][fC][mU][mU][mC][mA][fU][fG][fC][mA][fG][fG][mG][mU][mU][fA][mC][mA][mA][mG][mC][mA][mG][mC][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc]	277	[Phosphonate-4O-mUs][fUs][fGs][mU][fA][mA][fC][fC][mC][fU][mG][fC][mA][fU][mG][fA][mA][mG][fC][mUs][mGs][mG]	278

	GalNAc][mG][mG][mC][mU][mG][mC]			
55	[mCs][mU][fG][mG][mA][mG][mC][fA][fC][fC][mG][fU][fU][mA][mA][mG][fG][mA][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	279	[Phosphonate-4O-mUs][fGs][fUs][mC][fC][mU][fU][fA][mA][fC][mG][fG][mU][fG][mC][fU][mC][mC][fA][mGs][mGs][mG]	280
56	[mGs][mC][fA][mC][mC][mG][mU][fU][fA][fA][mG][fG][fA][mC][mA][mA][fG][mU][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	281	[Phosphonate-4O-mUs][fAs][fAs][mC][fU][mU][fG][fU][mC][fC][mU][fU][mA][fA][mC][fG][mG][mU][fG][mCs][mGs][mG]	282
57	[mUs][mG][fU][mA][mG][mG][mU][fU][fG][fC][mU][fU][fA][mA][mA][mA][fG][mG][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	283	[Phosphonate-4O-mUs][fCs][fCs][mC][fU][mU][fU][fU][mA][fA][mG][fC][mA][fA][mC][fC][mU][mA][fC][mAs][mGs][mG]	284
58	[mGs][mU][fU][mG][mC][mU][mU][fA][fA][fA][mA][fG][fG][mG][mA][mC][fA][mG][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	285	[Phosphonate-4O-mUs][fAs][fCs][mU][fG][mU][fC][fC][mC][fU][mU][fU][mU][fA][mA][fG][mC][mA][fA][mCs][mGs][mG]	286
59	[mGs][mA][fG][mC][fA][mC][mC][fG][fU][fU][fA][mA][fG][mG][fA][	287	[Phosphonate-4O-mUs][fCs][fUs][mU][fG][mU][fC][mC][mU][fU][mA][f	288

	mC][fA][mA][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]		A][mC][fG][mG][fU][fG][mC][fU][mCs][mGs][mG]	
60	[mAs][mG][fC][mA][fC][mC][mG][fU][fU][fA][fA][mG][fG][mA][fC][mA][fA][mG][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	289	[Phosphonate-4O-mUs][fAs][fCs][mU][fU][mG][fU][mC][mC][fU][mU][fA][mA][fC][mG][fG][fU][mG][fC][mUs][mGs][mG]	290
61	[mCs][mU][fG][mU][fA][mG][mG][fU][fU][fG][fC][mU][fU][mA][fA][mA][fA][mG][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	291	[Phosphonate-4O-mUs][fCs][fCs][mU][fU][mU][fU][mA][mA][fG][mC][fA][mA][fC][mC][fU][fA][mC][fA][mGs][mGs][mG]	292
62	[mAs][mG][fG][mU][fU][mG][mC][fU][fU][fA][fA][mA][fA][mG][fG][mG][fA][mC][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	293	[Phosphonate-4O-mUs][fUs][fGs][mU][fC][mC][fC][mU][mU][fU][mU][fA][mA][fG][mC][fA][fA][mC][fC][mUs][mGs][mG]	294
63	[mGs][mG][fU][mU][fG][mC][mU][fU][fA][fA][fA][mA][fG][mG][fG][mA][fC][mA][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	295	[Phosphonate-4O-mUs][fCs][fUs][mG][fU][mC][fC][mC][mU][fU][mU][fU][mA][fA][mG][fC][fA][mA][fC][mCs][mGs][mG]	296

	GalNAc][prgA-peg-GalNAc][mG][mC][mU][mG][mC]			
64	[mCs][mC][fA][mA][fU][mA][mA][fA][fG][fC][fU][mG][fG][mA][fC][mA][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	297	[Phosphonate-4O-mUs][fUs][fCs][mU][fU][mG][fU][mC][mC][fA][mG][fC][mU][fU][mU][fA][fU][mU][fG][mGs][mGs][mG]	298
65	[mAs][mU][fG][mG][fC][mU][mU][fC][fA][fG][fU][mU][fC][mC][fC][mU][fG][mA][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	299	[Phosphonate-4O-mUs][fUs][fUs][mC][fA][mG][fG][mG][mA][fA][mC][fU][mG][fA][mA][fG][fC][mC][fA][mUs][mGs][mG]	300
66	[mGs][mC][fU][mU][fC][mA][mG][fU][fU][fC][fC][mC][fU][mG][fA][mA][fA][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	301	[Phosphonate-4O-mUs][fUs][fCs][mU][fU][mU][fC][mA][mG][fG][mG][fA][mA][fC][mU][fG][fA][mA][fG][mCs][mGs][mG]	302
67	[mCs][mA][fG][mU][fU][mC][mC][fC][fU][fG][fA][mA][fA][mG][fA][mC][fU][mA][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	303	[Phosphonate-4O-mUs][fGs][fUs][mA][fG][mU][fC][mU][mU][fU][mC][fA][mG][fG][mG][fA][fA][mC][fU][mGs][mGs][mG]	304
68	[mAs][mG][fU][mU][fC][mC][mC][fU][fG][fA]	305	[Phosphonate-4O-mUs][fAs][fGs][mU][fA][m	306

	[fA][mA][fG][mA][fC][mU][fA][mC][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]		G][fU][mC][mU][fU][mU][fC][mA][fG][mG][fG][fA][mA][fC][mUs][mGs][mG]	
69	[mCs][mC][fU][mG][fA][mA][mA][fG][fA][fC][fU][mA][fC][mU][fG][mG][fA][mG][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	307	[Phosphonate-4O-mUs][fGs][fCs][mU][fC][mC][fA][mG][mU][fA][mG][fU][mC][fU][mU][fU][fC][mA][fG][mGs][mGs][mG]	308
70	[mGs][mA][fA][mA][fG][mA][mC][fU][fA][fC][fU][mG][fG][mA][fG][mC][fA][mC][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	309	[Phosphonate-4O-mUs][fGs][fGs][mU][fG][mC][fU][mC][mC][fA][mG][fU][mA][fG][mU][fC][fU][mU][fU][mCs][mGs][mG]	310
71	[mGs][mA][fC][mU][fA][mC][mU][fG][fG][fA][fG][mC][fA][mC][fC][mG][fU][mU][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	311	[Phosphonate-4O-mUs][fUs][fAs][mA][fC][mG][fG][mU][mG][fC][mU][fC][mC][fA][mG][fU][fA][mG][fU][mCs][mGs][mG]	312
72	[mAs][mC][fU][mG][fG][mA][mG][fC][fA][fC][fC][mG][fU][mU][fA][mA][fG][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-	313	[Phosphonate-4O-mUs][fUs][fCs][mC][fU][mU][fA][mA][mC][fG][mG][fU][mG][fC][mU][fC][fC][mA][fG][mUs][mGs][mG]	314

	GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mC][mU][mG][mC]			
73	[mGs][mG][fA][mG][fC][mA][mC][fC][fG][fU][fU][mA][fA][mG][fG][mA][fC][mA][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	315	[Phosphonate-4O-mUs][fUs][fUs][mG][fU][mC][fC][mU][mU][fA][mA][fC][mG][fG][mU][fG][fC][mU][fC][mCs][mGs][mG]	316
74	[mGs][mC][fU][mU][fC][mA][mU][fG][fC][fA][fG][mG][fG][mU][fU][mA][fC][mA][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	317	[Phosphonate-4O-mUs][fAs][fUs][mG][fU][mA][fA][mC][mC][fC][mU][fG][mC][fA][mU][fG][fA][mA][fG][mCs][mGs][mG]	318
75	[mCs][mA][fC][mC][fG][mU][mU][fA][fA][fG][fG][mA][fC][mA][fA][mG][fU][mU][mC][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	319	[Phosphonate-4O-mUs][fGs][fAs][mA][fC][mU][fU][mG][mU][fC][mC][fU][mU][fA][mA][fC][fG][mG][fU][mGs][mGs][mG]	320
76	[mAs][mC][fA][mA][fG][mU][mU][fC][fU][fC][fU][mG][fA][mG][fU][mU][fC][mU][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	321	[Phosphonate-4O-mUs][fCs][fAs][mG][fA][mA][fC][mU][mC][fA][mG][fA][mG][fA][mA][fC][fU][mU][fG][mUs][mGs][mG]	322

77	[mAs][mA][fG][mU][mU][mC][mU][fC][fU][fG][mA][fG][fU][mU][mC][mU][fG][mG][mG][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	323	[Phosphonate-4O-mUs][fCs][fCs][mC][fA][mG][fA][fA][mC][fU][mC][fA][mG][fA][mG][fA][mA][mC][fU][mUs][mGs][mG]	324
78	[mAs][mG][fU][mU][mC][mU][mC][fU][fG][fA][mG][fU][fU][mC][mU][mG][fG][mG][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	325	[Phosphonate-4O-mUs][fUs][fCs][mC][fC][mA][fG][fA][mA][fC][mU][fC][mA][fG][mA][fG][mA][mA][fC][mUs][mGs][mG]	326
79	[mGs][mU][fU][mC][mU][mC][mU][fG][fA][fG][mU][fU][fC][mU][mG][mG][fG][mA][mU][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	327	[Phosphonate-4O-mUs][fAs][fUs][mC][fC][mC][fA][fG][mA][fA][mC][fU][mC][fA][mG][fA][mG][mA][fA][mCs][mGs][mG]	328
80	[mGs][mG][fA][mC][mC][mC][mU][fG][fA][fG][mG][fU][fC][mA][mG][mA][fC][mC][mA][mA][mG][mC][mA][mG][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]	329	[Phosphonate-4O-mUs][fUs][fGs][mG][fU][mC][fU][fG][mA][fC][mC][fU][mC][fA][mG][fG][mG][mU][fC][mCs][mGs][mG]	330
81	[mGs][mU][fA][mU][mU][mC][mU][fC][fA][fG][mU][fG][fC][mU][mC][mU][fC][mC][mU][mA][mG][mC][mA][m	331	[Phosphonate-4O-mUs][fAs][fGs][mG][fA][mG][fA][fG][mC][fA][mC][fU][mG][fA][mG][fA][mA][mU][fA][mCs][mGs][mG]	332

	G][mC][mC][prgG-peg-GalNAc][prgA-peg-GalNAc][prgA-peg-GalNAc][mG][mG][mC][mU][mG][mC]			
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[00264] SEQ ID NO:333 – Artificial Sequence
GCAGCCGAAAGGCUGC

[00265] SEQ ID NO:334 – Target Sequence 1
TTCAGTTCCTGAAAGACTA

[00266] SEQ ID NO:335 – Target Sequence 2
TGGAGCACCGTTAAGGACAA

[00267] SEQ ID NO:336 – Target Sequence 3
ACCGTTAAGGACAAGTTCT

[00268] SEQ ID NO:337 – Target Sequence 4
GCTGCCCCTGTAGGTTGCT

[00269] SEQ ID NO:338 – Target Sequence 5
GTAGGTTGCTTAAAAGGGA

[00270] SEQ ID NO:339 – Target Sequence 6
CTTAAAAGGGACAGTATTC

[00271] SEQ ID NO:340 – Target Sequence 7
AAAAGGGACAGTATTCTCA

[00272] SEQ ID NO:341 – Target Sequence 8
GACAGTATTCTCAGTGCTC

CLAIMS

1. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.
2. The RNAi oligonucleotide of Claim 1, wherein the sense strand is 15 to 50 nucleotides in length.
3. The RNAi oligonucleotide of Claims 1 or 2, wherein the sense strand is 18 to 36 nucleotides in length.
4. The RNAi oligonucleotide of any one of Claims 1 to 3, wherein the antisense strand is 15 to 30 nucleotides in length.
5. The RNAi oligonucleotide of any one of Claims 1 to 4, wherein the antisense strand is 22 nucleotides in length, and where in the antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length.
6. The RNAi oligonucleotide of any one of Claims 1 to 5, wherein the region of complementarity is at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.
7. The RNAi oligonucleotide of any one of Claims 1 to 6, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.
8. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence

of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

9. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

10. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

11. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

12. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

13. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense

strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to an APOC3 mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

14. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to an APOC3 mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

15. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to an APOC3 mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

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

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

18. The RNAi oligonucleotide of Claim 17, wherein the tetraloop comprises a sequence of 5'-GAAA-3'.
19. The RNAi oligonucleotide of any one of Claims 13 to 18, wherein S1 and S2 are 1-10 nucleotides in length and have the same length.
20. The RNAi oligonucleotide of Claim 19, wherein S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length.
21. The RNAi oligonucleotide of Claim 20, wherein S1 and S2 are 6 nucleotides in length.
22. The RNAi oligonucleotide of any one of Claims 13 to 21, wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:333).
23. The RNAi oligonucleotide of any one of Claims 1 to 22, wherein the antisense strand comprises a 3' overhang sequence of 1 or more nucleotides in length.
24. The RNAi oligonucleotide of Claim 23, wherein the 3' overhang sequence is 2 nucleotides in length, and optionally wherein the 3' overhang sequence is GG.
25. The RNAi oligonucleotide of any one of the preceding claims comprising at least 1 modified nucleotide.
26. The RNAi oligonucleotide of any one of Claims 13 to 25, wherein all nucleotides of the oligonucleotide are modified except the nucleotides in the loop of the stem-loop.
27. The RNAi oligonucleotide of Claim 25 or 26, wherein the modified nucleotide comprises a 2'-modification.
28. The RNAi oligonucleotide of Claim 27, wherein the 2'-modification is a modification selected from the group consisting of 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid.

29. The RNAi oligonucleotide of any one of Claims 25 to 28, wherein all nucleotides comprising the RNAi oligonucleotide are modified, and optionally wherein the modification is a 2'-modification selected from the group consisting of 2'-fluoro and 2'-O-methyl.

30. The RNAi oligonucleotide of Claim 29, wherein one or more nucleotides at positions 8, 9, 10, or 11 of the sense strand are modified with 2'-fluoro.

31. The RNAi oligonucleotide of Claim 29 or 30, wherein one or more nucleotides at positions 2, 3, 4, 5, 7, 10, or 14 of the antisense strand are modified with 2'-fluoro.

32. The RNAi oligonucleotide of any one of Claims 29 or 31, wherein one or more nucleotides at positions 1, 2, 3, 4, 5, 6, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 31, 32, 33, 34, 35, or 36 of the sense strand are modified with 2'-O-methyl.

33. The RNAi oligonucleotide of any one of Claims 29 to 32, wherein one or more nucleotides at positions 1, 6, 8, 9, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, or 22 of the antisense strand are modified with 2'-O-methyl.

34. The RNAi oligonucleotide of any one of the preceding claims comprising at least one modified internucleotide linkage.

35. The RNAi oligonucleotide of Claim 34, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

36. The RNAi oligonucleotide of Claim 35, wherein the internucleotide linkage of nucleotides at positions 1 and 2 of the sense strand are modified with the phosphorothioate linkage.

37. The RNAi oligonucleotide of Claim 35 or 36, wherein the internucleotide linkage of one or more nucleotides at positions 1 and 2, 2 and 3, 3 and 4, 20 and 21, or 21 and 22 of the antisense strand are modified with the phosphorothioate linkage.

38. The RNAi oligonucleotide of any one of Claims 1 to 24, wherein the RNAi oligonucleotide has a modification pattern as shown in FIG. 1A, FIG. 1B, or FIG. 1C.
39. The RNAi oligonucleotide of Claim 38, wherein the RNAi oligonucleotide has the modification pattern shown in FIG. 1B.
40. The RNAi oligonucleotide of any one of the preceding claims, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.
41. The RNAi oligonucleotide of Claim 40, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonyl phosphonate, and optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.
42. The RNAi oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.
43. The RNAi oligonucleotide of Claim 42, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.
44. The RNAi oligonucleotide of Claim 43, wherein each targeting ligand comprises a N-acetyl galactosamine (GalNAc) moiety.
45. The RNAi oligonucleotide of Claim 43, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.
46. The RNAi oligonucleotide of any one of Claims 16 to 41, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.
47. The RNAi oligonucleotide of any one of the preceding claims, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs:9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119,

121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, and 169.

48. The RNAi oligonucleotide of any one of the preceding claims, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs:10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, and 170.

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

- (a) SEQ ID NOs:37 and 38,
- (b) SEQ ID NOs:43 and 44,
- (c) SEQ ID NOs:45 and 46,
- (d) SEQ ID NOs:87 and 88,
- (e) SEQ ID NOs:89 and 90,
- (f) SEQ ID NOs:99 and 100,
- (g) SEQ ID NOs:101 and 102, and
- (h) SEQ ID NOs:105 and 106.

50. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:37 and wherein the antisense strand is SEQ ID NO:38.

51. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:43 and wherein the antisense strand is SEQ ID NO:44.

52. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:45, and wherein the antisense strand is SEQ ID NO:46.

53. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:87 and wherein the antisense strand is SEQ ID NO:88.

54. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:89, and wherein the antisense strand is SEQ ID NO:90.
55. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:99, and wherein the antisense strand is SEQ ID NO:100.
56. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:101, and wherein the antisense strand is SEQ ID NO:102.
57. The RNAi oligonucleotide of Claim 49, wherein the sense strand is SEQ ID NO:105, and wherein the antisense strand is SEQ ID NO:106.
58. The RNAi oligonucleotide of any one of Claims 1 and 8 to 15, wherein the sense strand and the antisense strands comprise nucleotide sequences selected from the group consisting of:
- (a') SEQ ID NOs:199 and 200,
 - (b') SEQ ID NOs:205 and 206,
 - (c') SEQ ID NOs:207 and 208,
 - (d') SEQ ID NOs:249 and 250,
 - (e') SEQ ID NOs:251 and 252,
 - (f') SEQ ID NOs:261 and 262,
 - (g') SEQ ID NOs:263 and 264, and
 - (h') SEQ ID NOs:267 and 268.
59. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:199 and the antisense strand is SEQ ID NO:200.
60. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:205 and the antisense strand is SEQ ID NO:206.
61. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:207 and the antisense strand is SEQ ID NO:208.

62. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:249 and the antisense strand is SEQ ID NO:250.
63. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:251 and the antisense strand is SEQ ID NO:252.
64. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:261 and the antisense strand is SEQ ID NO:262.
65. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:263 and the antisense strand is SEQ ID NO:264.
66. The RNAi oligonucleotide of Claim 58, wherein the sense strand is SEQ ID NO:267 and the antisense strand is SEQ ID NO:268.
67. The RNAi oligonucleotide of any one of Claims 58 to 66, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.
68. The RNAi oligonucleotide of Claim 67, wherein each targeting ligand is a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.
69. The RNAi oligonucleotide of Claim 68, wherein each targeting ligand comprises a N-acetyl galactosamine (GalNAc) moiety.
70. The RNAi oligonucleotide of Claim 69, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.
71. The RNAi oligonucleotide of Claim 69, wherein a sequence of 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:333) in the sense strand forms a stem-loop structure, and wherein nucleotides in a sequence of 5'-GAAA-3' in the loop are each conjugated to a monovalent GalNAc moiety.

72. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOs:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

73. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOs:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

74. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOs:334 to 341, and wherein the region of complementarity is at least 19 contiguous nucleotides in length.

75. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise 1 or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region

of complementarity to an APOC3 mRNA target sequence of any one of SEQ ID NOs:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

76. The RNAi oligonucleotide of any one of Claims 72 to 75, wherein the sense strand comprises of any one of SEQ ID NOs:37, 43, 45, 87, 89, 99, 101, and 105; or wherein the sense strand comprises of any one of SEQ ID NOs:199, 205, 207, 249, 251, 261, 263, and 267.

77. The RNAi oligonucleotide of any one of Claims 72 to 76, wherein the antisense strand comprises of any one of SEQ ID NOs:38, 44, 46, 88, 90, 100, 102, and 106; or wherein the antisense strand comprises of any one of SEQ ID NOs:200, 206, 208, 250, 252, 262, 264, and 268.

78. The RNAi oligonucleotide of any one of Claims 72 to 77, wherein the sense strand and antisense strands are selected from the group consisting of:

- (a) SEQ ID NOs:37 and 38,
- (b) SEQ ID NOs:43 and 44,
- (c) SEQ ID NOs:45 and 46,
- (d) SEQ ID NOs:87 and 88,
- (e) SEQ ID NOs:89 and 90,
- (f) SEQ ID NOs:99 and 100,
- (g) SEQ ID NOs:101 and 102, and
- (h) SEQ ID NOs:105 and 106; or
- (a') SEQ ID NOs:199 and 200,
- (b') SEQ ID NOs:205 and 206,
- (c') SEQ ID NOs:207 and 208,
- (d') SEQ ID NOs:249 and 250,
- (e') SEQ ID NOs:251 and 252,
- (f') SEQ ID NOs:261 and 262,
- (g') SEQ ID NOs:263 and 264, and
- (h') SEQ ID NOs:267 and 268.

79. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:199 and the antisense strand is SEQ ID NO:200.

80. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:205 and the antisense strand is SEQ ID NO:206.
81. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:207 and the antisense strand is SEQ ID NO:208.
82. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:249 and the antisense strand is SEQ ID NO:250.
83. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:251 and the antisense strand is SEQ ID NO:252.
84. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:261 and the antisense strand is SEQ ID NO:262.
85. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:263 and the antisense strand is SEQ ID NO:264.
86. The RNAi oligonucleotide of Claim 78, wherein the sense strand is SEQ ID NO:267 and the antisense strand is SEQ ID NO:286.
87. The RNAi oligonucleotide of any one of Claims 72 to 86, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.
88. The RNAi oligonucleotide of Claim 87, wherein each targeting ligand is a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.
89. The RNAi oligonucleotide of Claim 88, wherein each targeting ligand comprises a N-acetyl galactosamine (GalNAc) moiety.

90. The RNAi oligonucleotide of Claim 89, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

91. The RNAi oligonucleotide of Claim 89, wherein a sequence of 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:333) in the sense strand forms a stem-loop structure, and wherein nucleotides in a sequence of 5'-GAAA-3' in the loop are each conjugated to a monovalent GalNAc moiety.

92. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, and wherein the sense strand and the antisense strand consist of sequences selected from the group consisting of:

- (a') SEQ ID NOs:199 and 200,
- (b') SEQ ID NOs:205 and 206,
- (c') SEQ ID NOs:207 and 208,
- (d') SEQ ID NOs:249 and 250,
- (e') SEQ ID NOs:251 and 252,
- (f') SEQ ID NOs:261 and 262,
- (g') SEQ ID NOs:263 and 264, and
- (h') SEQ ID NOs:267 and 268.

93. The RNAi oligonucleotide of Claim 92, wherein a sequence of 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:333) in the sense strand forms a stem-loop structure, and wherein nucleotides in a sequence of 5'-GAAA-3' in the loop are each conjugated to a monovalent GalNAc moiety.

94. A pharmaceutical composition comprising:
the RNAi oligonucleotide of any one of Claims 1 to 93, or a pharmaceutically acceptable salt thereof; and
a pharmaceutically acceptable carrier, delivery agent or excipient.

95. A method of delivering an oligonucleotide to an individual, the method comprising the step of:

administering the pharmaceutical composition of Claim 94 to the individual.

96. A method of treating an individual having a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, the method comprising the step of:

administering to the individual a therapeutically effective amount of the RNAi oligonucleotide of any one of Claims 1 to 93, or the pharmaceutical composition of Claim 94, thereby treating the individual.

97. A method of reducing apolipoprotein C-III (*APOC3*) expression in a cell, a population of cells or an individual, the method comprising the step of:

contacting the cell or the population of cells with the RNAi oligonucleotide of any one of Claims 1 to 93 or the pharmaceutical composition of Claim 94; or

administering to the individual the RNAi oligonucleotide of any one of Claims 1 to 93 or the pharmaceutical composition of Claim 94.

98. The method of Claim 97, wherein reducing *APOC3* expression comprises reducing an amount or level of *APOC3* mRNA, an amount or level of *APOC3* protein, or both.

99. The method of Claim 97 or 98, wherein the individual has a disease, disorder or condition associated with *APOC3* expression.

100. The method of Claim 99, wherein the disease, disorder or condition associated with *APOC3* expression is acute coronary diseases (ACD), atherosclerotic cardiovascular disease (ASCVD), alcoholic hepatitis (AH), alcoholic liver disease (ALD), cardiometabolic disease, cholangiocarcinoma (CCA), cirrhosis, coronary heart diseases (CHD), diabetes, hepatic fibrosis, hepatic inflammation, hepatocellular carcinoma (HCC), hyperlipidemia, hypertriglyceridemia, high non-HDL cholesterol, insulin resistance, liver steatosis, metabolic syndromes (MetS), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), obesity, or primary sclerosing cholangitis (PSC).

101. The method of any one of Claims 96 to 100, wherein the RNAi oligonucleotide or the pharmaceutical composition is administered in combination with a second composition or therapeutic agent.

102. A method of treating an individual having a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, the method comprising the step of:

administering to the individual a therapeutically effective amount of a RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to an *APOC3* mRNA target sequence of any one of SEQ ID NOS:334 to 341, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

103. A method of treating an individual having a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, the method comprising the step of:

administering to the individual a therapeutically effective amount of a RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in Table 2 or Table 3, or a pharmaceutical composition thereof, thereby treating the individual.

104. A method of treating an individual having a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, the method comprising the step of:

administering to the individual a therapeutically effective amount of a RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOS:37 and 38,
- (b) SEQ ID NOS:43 and 44,
- (c) SEQ ID NOS:45 and 46,
- (d) SEQ ID NOS:87 and 88,
- (e) SEQ ID NOS:89 and 90,
- (f) SEQ ID NOS:99 and 100,
- (g) SEQ ID NOS:101 and 102, and
- (h) SEQ ID NOS:105 and 106; or
- (a') SEQ ID NOS:199 and 200,
- (b') SEQ ID NOS:205 and 260,

- (c') SEQ ID NOs:207 and 208,
- (d') SEQ ID NOs:249 and 250,
- (e') SEQ ID NOs:251 and 252,
- (f') SEQ ID NOs:261 and 262,
- (g') SEQ ID NOs:263 and 264, and
- (h') SEQ ID NOs:267 and 268.

105. A method of treating an individual having a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, the method comprising the step of:

administering to the individual a therapeutically effective amount of a RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand are selected from the group consisting of:

- (a) SEQ ID NOs:37 and 38,
- (b) SEQ ID NOs:43 and 44,
- (c) SEQ ID NOs:45 and 46,
- (d) SEQ ID NOs:87 and 88,
- (e) SEQ ID NOs:89 and 90,
- (f) SEQ ID NOs:99 and 100,
- (g) SEQ ID NOs:101 and 102, and
- (h) SEQ ID NOs:105 and 106; or
- (a') SEQ ID NOs:199 and 200,
- (b') SEQ ID NOs:205 and 260,
- (c') SEQ ID NOs:207 and 208,
- (d') SEQ ID NOs:249 and 250,
- (e') SEQ ID NOs:251 and 252,
- (f') SEQ ID NOs:261 and 262,
- (g') SEQ ID NOs:263 and 264, and
- (h') SEQ ID NOs:267 and 268.

106. The method of Claim 105, wherein the sense strand is SEQ ID NO:199 and the antisense strand is SEQ ID NO:200.

107. The method of Claim 105, wherein the sense strand is SEQ ID NO:205 and the antisense strand is SEQ ID NO:206.

108. The method of Claim 105, wherein the sense strand is SEQ ID NO:207 and the antisense strand is SEQ ID NO:208.

109. The method of Claim 15, wherein the sense strand is SEQ ID NO:249 and the antisense strand is SEQ ID NO:250.

110. The method of Claim 105, wherein the sense strand is SEQ ID NO:251 and the antisense strand is SEQ ID NO:252.

111. The method of Claim 105, wherein the sense strand is SEQ ID NO:261 and the antisense strand is SEQ ID NO:262.

112. The method of Claim 75, wherein the sense strand is SEQ ID NO:263 and the antisense strand is SEQ ID NO:264.

113. The method of Claim 75, wherein the sense strand is SEQ ID NO:267 and the antisense strand is SEQ ID NO:268.

114. The method of any one of Claims 105 to 113, wherein the disease, disorder or condition associated with *APOC3* expression is selected from the group consisting of acute coronary diseases (ACD), atherosclerotic cardiovascular disease (ASCVD), alcoholic hepatitis (AH), alcoholic liver disease (ALD), cardiometabolic disease, cholangiocarcinoma (CCA), cirrhosis, coronary heart diseases (CHD), diabetes, hepatic fibrosis, hepatic inflammation, hepatocellular carcinoma (HCC), hyperlipidemia, hypertriglyceridemia, high non-HDL cholesterol, insulin resistance, liver steatosis, metabolic syndromes (MetS), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), obesity, or primary sclerosing cholangitis (PSC).

115. Use of the RNAi oligonucleotide of any one of Claims 1 to 93, or the pharmaceutical composition of Claim 94, in the manufacture of a medicament for the treatment of a disease,

disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, optionally for the treatment of acute coronary diseases (ACD), atherosclerotic cardiovascular disease (ASCVD), alcoholic hepatitis (AH), alcoholic liver disease (ALD), cardiometabolic disease, cholangiocarcinoma (CCA), cirrhosis, coronary heart diseases (CHD), diabetes, hepatic fibrosis, hepatic inflammation, hepatocellular carcinoma (HCC), hyperlipidemia, hypertriglyceridemia, high non-HDL cholesterol, insulin resistance, liver steatosis, metabolic syndromes (MetS), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), obesity, or primary sclerosing cholangitis (PSC).

116. The RNAi oligonucleotide of any one of Claims 1 to 93, or the pharmaceutical composition of Claim 94, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression, optionally for the treatment of acute coronary diseases (ACD), atherosclerotic cardiovascular disease (ASCVD), alcoholic hepatitis (AH), alcoholic liver disease (ALD), cardiometabolic disease, cholangiocarcinoma (CCA), cirrhosis, coronary heart diseases (CHD), diabetes, hepatic fibrosis, hepatic inflammation, hepatocellular carcinoma (HCC), hyperlipidemia, hypertriglyceridemia, high non-HDL cholesterol, insulin resistance, liver steatosis, metabolic syndromes (MetS), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), obesity, or primary sclerosing cholangitis (PSC).

117. A kit comprising the RNAi oligonucleotide of any one of Claims 1 to 93, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to an individual having a disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression.

118. The use of Claim 115, the RNAi oligonucleotide or pharmaceutical composition for use, or adaptable for use, of Claim 116, or the kit of Claim 117, wherein the disease, disorder or condition associated with apolipoprotein C-III (*APOC3*) expression is acute coronary diseases (ACD), atherosclerotic cardiovascular disease (ASCVD), alcoholic hepatitis (AH), alcoholic liver disease (ALD), cardiometabolic disease, cholangiocarcinoma (CCA), cirrhosis, coronary heart diseases (CHD), diabetes, hepatic fibrosis, hepatic inflammation, hepatocellular carcinoma (HCC), hyperlipidemia, hypertriglyceridemia, high non-HDL cholesterol, insulin resistance, liver steatosis, metabolic syndromes (MetS), non-alcoholic fatty liver disease

(NAFLD), non-alcoholic steatohepatitis (NASH), obesity, or primary sclerosing cholangitis (PSC).

119. A RNAi oligonucleotide for reducing apolipoprotein C-III (*APOC3*) expression, the oligonucleotide having a sense strand and an antisense strand that are optionally modified, wherein the sense strand and the antisense strand form a duplex region, wherein the sense strand and the antisense strand are a pair selected from the group consisting of:

- (a) SEQ ID NOs:37 and 38,
- (b) SEQ ID NOs:43 and 44,
- (c) SEQ ID NOs:45 and 46,
- (d) SEQ ID NOs:87 and 88,
- (e) SEQ ID NOs:89 and 90,
- (f) SEQ ID NOs:99 and 100,
- (g) SEQ ID NOs:101 and 102, and
- (h) SEQ ID NOs:105 and 106, respectively,

wherein a sequence of 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:333) in the sense strand forms a stem-loop structure, and wherein nucleotides in a sequence of 5'-GAAA-3' in the loop are each conjugated to a monovalent GalNAc moiety.

120. The RNAi oligonucleotide of Claim 119, wherein the sense strand and the antisense strand are optionally modified and are a pair selected from the group consisting of:

- (a') SEQ ID NOs:199 and 200,
- (b') SEQ ID NOs:205 and 260,
- (c') SEQ ID NOs:207 and 208,
- (d') SEQ ID NOs:249 and 250,
- (e') SEQ ID NOs:251 and 252,
- (f') SEQ ID NOs:261 and 262,
- (g') SEQ ID NOs:263 and 264, and
- (h') SEQ ID NOs:267 and 268, respectively.