

NOVEL RNA THERAPEUTICS AND USES THEREOF

The present disclosure relates to novel RNAi agents designed to decrease the expression of ANGPTL8 in the liver, where the RNAi agents comprise delivery moieties
5 conjugated to oligonucleotides optionally via a linker. The RNAi agents are useful in the treatment of diseases involving the regulation of ANGPTL8 expression.

Angiopoietin-like protein 8 (ANGPTL8) is mainly expressed in liver and adipose tissue and it plays an important role in triglyceride metabolism. ANGPTL8, together with
10 ANGPTL3 or ANGPTL4, is thought to regulate triglyceride levels by inhibiting the enzymatic activity of lipoprotein lipase (LPL), which, when active, hydrolyzes triglycerides and decreases circulating plasma triglycerides. Increased levels of ANGPTL8 are observed or associated with cardiovascular disease, diabetes, dyslipidemia (including high triglyceride levels), aberrant renal function, hypertension, nonalcoholic fatty liver disease such as nonalcoholic steatohepatitis (NASH), and obesity.

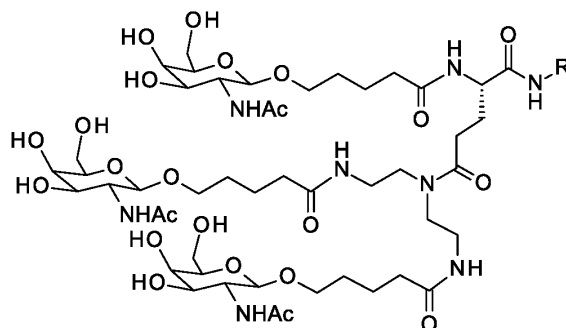
15 The RNAi agents, such as those disclosed herein, permit targeting genes in a sequence-specific manner for personalized treatment of many different types of diseases involving gene dysregulation. Compounds comprising oligonucleotides, such as the RNAi agents herein, can work via different mechanisms depending on the particular type of oligonucleotides employed. RNA interference molecules, including the RNAi agents
20 disclosed herein, typically operate to knock down, or decrease, gene expression of a given target transcript, thereby decreasing the level of protein. By delivering RNAi molecules, such as the RNAi agents herein, to a desired tissue of the patient, gene expression can be decreased in a tissue specific manner.

RNAi agents comprising N-acetylgalactose (GalNAc) to target the asialoglycoprotein
25 receptor on liver cells are one example. Specifically, givosiran is an FDA approved siRNA that targets ALAS1 gene transcript to treat acute hepatic porphyria, employs a delivery moiety comprising GalNAc for entry into liver cells. Inclisiran is an FDA approved siRNA that targets the PCSK9 gene transcript to lower LDL cholesterol, and also employs a delivery moiety comprising GalNAc for entry into liver cells. RNAi molecules comprising siRNAs

targeting ANGPTL8 have been described, e.g., WO2020104649. However, only four siRNA molecules are approved for use in humans, and no therapeutic siRNAs targeting ANGPTL8 are yet approved. Moreover, limited information is available preclinically and clinically about the ideal attributes for a therapeutic siRNA in vivo, especially for diseases of the liver or involving the liver such as cardiovascular disease, dyslipidemia, e.g. high triglycerides, and inflammatory liver diseases.

There remains a need to provide alternative RNAi agents comprising a delivery moiety comprising GalNAc and one or more oligonucleotides to decrease ANGPTL8 expression. More particularly, there is a need to provide RNAi agents comprising a novel GalNAc delivery moiety and a sense strand and an antisense strand, wherein the antisense strand is complementary to ANGPTL8 mRNA, wherein such an RNAi agent exhibits one or more of: improved tissue exposure, suitably improved exposure in the liver; improved liver to kidney exposure ratios; improved knockdown; an improved durable response; an improved pharmacokinetic profile; fewer off target effects; an improved toxicity profile; an improved safety profile, fewer side effects, improved tolerability, improved control of cholesterol and/or triglyceride levels in a patient, improved cardiovascular risk profile in a patient, improved and/or simplified synthesis, synthetic processes with fewer degradation products, or any combination thereof.

In one embodiment of the present disclosure is an RNA interference (RNAi) agent comprising a delivery moiety of Formula I:



Formula I,

wherein R comprises a sense strand and an antisense strand, and wherein the antisense strand

5 comprises at least 15 contiguous nucleotides of a sequence that is complementary to the mRNA transcript of ANGPTL8, and wherein the sense strand and the antisense strand form a region of complementarity of at least 15 nucleotides, and wherein the sense strand and antisense strand are each independently 15 to 30 nucleotides in length, and optionally wherein the sense strand and antisense strand each independently comprise one or more

10 modified nucleotides, and optionally wherein the sense strand and the antisense strand each independently comprise one or more modified internucleotide linkages, and wherein R is optionally conjugated to Formula I via a linker. In another embodiment, the antisense strand comprises at least 15 contiguous nucleotides of a sequence that is complementary to SEQ ID NO:1. In a further embodiment, the sense strand and antisense strand are each independently

15 18 to 23 nucleotides in length. In a further embodiment of any of these RNAi agents, the antisense strand forms a region of complementarity of at least 18 nucleotides to the mRNA transcript of ANGPTL8. In a different further embodiment of any of these RNAi agents, the antisense strand forms a region of complementarity of at least 18 nucleotides to SEQ ID NO:1.

20 In a further embodiment is an RNAi agent wherein the antisense strand comprises at least 15 nucleotides of a sequence selected from the group consisting of SEQ ID NO:s 405-

525. In yet a further embodiment, the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525.

In a further embodiment of the RNAi agents disclosed herein, the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group
5 consisting of SEQ ID NOs: 405, 408, 412, 413, 414, 415, 418, 420, 425, 426, 428, 429, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 448, 449, 451, 452, 454, 457, 458, 459, 463, 464, 465, 466, 467, 468, 469, 471, 472, 473, 474, 475, 476, 479, 490, 491, 492, 493, 495, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, and 509. In another embodiment, the antisense strand is selected from the group of antisense strand
10 sequences in Table 2.

In any of the embodiments of the RNAi agents disclosed herein, the RNAi agent of any the antisense strand is 23 nucleotides in length, or the sense strand is 21 nucleotides in length, or both.

In another embodiment of the RNAi agents disclosed herein, the antisense strand is
15 selected from the group consisting of SEQ ID NOs: 231-361, or a sequence having at least 90% sequence identity thereto. In other embodiments of the RNAi agents disclosed herein, the sense strand is selected from the group consisting of SEQ ID NOs: 124-230, or a sequence having at least 90% sequence identity thereto.

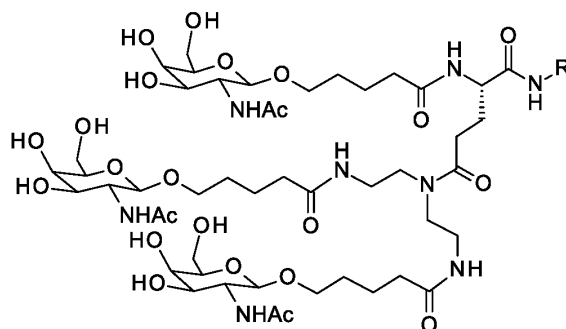
In further embodiments of any of the RNAi agents described herein, the region of
20 complementarity comprises 0, 1, 2, or 3 mismatches between the sense strand and the antisense strand.

In further embodiments of the RNAi agents, the sense strand and the antisense strand each independently comprise one or more modified nucleotides. In a further embodiment, the one or more modified nucleotides are independently 2' fluoro modified nucleotides or 2'-
25 O-methyl modified nucleotides. In other embodiments, each nucleotide of the sense strand and each nucleotide of the antisense strand is a modified nucleotide, and in further embodiment, each of the modified nucleotides are independently a 2' fluoro modified nucleotide or a 2'-O-methyl modified nucleotide.

In other embodiments of the RNAi agents herein, the sense strand and antisense strand each independently comprise one or more modified internucleotide linkages. In a further embodiment, each modified internucleotide linkage is a phosphorothioate linkage. In other embodiments, the sense strand and antisense strand each independently comprise four
 5 phosphorothioate linkages. In further embodiments, the first two 5' nucleotides of the sense strand and the two terminal 3' nucleotides of the sense strand are phosphorothioate linkages. In further embodiments, the first two 5' nucleotides of the antisense strand and the two terminal 3' nucleotides of the antisense strand are phosphorothioate linkages.

In other embodiments of the RNAi agents herein, the 5' nucleotide of the antisense
 10 strand comprises a phosphate group or a phosphate analog.

In another embodiment, the present disclosure provides an RNAi agent comprising a delivery moiety of Formula I conjugated to R:



15 Formula I;

wherein R comprises a sense strand and an antisense strand, and wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence that is complementary to the mRNA transcript of ANGPTL8, and wherein the sense strand and the antisense strand form a region of complementarity of at least 15 nucleotides, and wherein the sense strand and
 20 antisense strand are each independently 15 to 30 nucleotides in length, and optionally wherein the sense strand and antisense strand each independently comprise one or more modified nucleotides, and optionally wherein the sense strand and the antisense strand each

independently comprise one or more modified internucleotide linkages, and wherein R is optionally conjugated to a delivery moiety, D, of Formula I via a linker, L. In another embodiment, the antisense strand comprises at least 15 contiguous nucleotides of a sequence that is complementary to SEQ ID NO:1. In a further embodiment, the sense strand and
5 antisense strand are each independently 18 to 23 nucleotides in length. In a further embodiment of any of these RNAi agents, the antisense strand forms a region of complementarity of at least 18 nucleotides to the mRNA transcript of ANGPTL8. In a different further embodiment of any of these RNAi agents, the antisense strand forms a region of complementarity of at least 18 nucleotides to SEQ ID NO:1. In further
10 embodiments, wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525.

Any of the compounds herein, including the RNAi agents disclosed herein, comprising Formula I may have modifications or additions within Formula I, or the compounds may comprise additional moieties. For example, one or more alkyl chains in
15 Formula I may be extended or shortened, or the compound comprising Formula I may further comprise one or more oligonucleotides. The compounds herein comprising Formula I, such as the RNAi agents disclosed herein, are useful for, e.g. delivering one or more oligonucleotides, to a cell that has a receptor for one or more N-acetylgalactose (GalNAc, also N-GalNAc or galnac or Galnac) moieties, such as the asialoglycoprotein receptor
20 (ASPGR) that typically binds three GalNAc moieties. Accordingly, the compounds comprising Formula I herein, such as the RNAi agents disclosed herein, may be used to preferentially bind to liver cells that express ASPGR, thereby facilitating entry of the compounds into liver cells. As ASPGR is also present on adipose tissue, the compounds comprising Formula I, including the RNAi agents herein thus may be used to deliver
25 oligonucleotides to fat cells that express ASPGR.

In one embodiment is a compound or RNAi agent comprising a delivery moiety and one or more oligonucleotides, wherein the delivery moiety comprises Formula I, and wherein the oligonucleotides are complementary to the ANGPTL8 gene (hereinafter ANGPTL8 oligonucleotides). In a suitable further embodiment, the delivery moiety comprising Formula

I delivers the one or more ANGPTL8 oligonucleotides to liver tissue, by binding to the extracellular receptor ASPGR and permitting entry of the oligonucleotides into the cells that comprise the liver tissue. The ANGPTL8 oligonucleotides are also represented herein by R or a sense strand and/or antisense strand herein, including as set forth in the sense and
5 antisense sequences as set forth in the SEQ IDs herein.

The delivery moiety comprising Formula I can be used to deliver any number of ANGPTL8 oligonucleotides, such as the RNAi agents comprising R, including wherein R comprises a sense strand and/or an antisense strand disclosed herein, for diagnostic or, suitably, for therapeutic purposes. The one or more oligonucleotides such as the sense
10 strands and antisense strands disclosed herein may comprise DNA or RNA nucleotides or DNA or RNA nucleosides.

The oligonucleotides herein, including the antisense strands herein, are designed to target, that is, bind or anneal to, or form a regions of complementarity with, ANGPTL8 sequences in a cell to regulate gene expression, suitably decreasing ANGPTL8 gene
15 expression. In one embodiment is a compound or RNAi agent comprising Formula I disclosed herein, for decreasing expression of an ANGPTL8 transcript. In a further embodiment the compound or RNAi agent comprising Formula I disclosed herein for decreasing expression of an ANGPTL8 transcript further decreases ANGPTL8 protein expression. In another embodiment, the decrease in expression of a target transcript or target
20 protein is about 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 85, 80, 75, 70, 65, 60, 55, or 50 percent. In a further embodiment, the decrease in expression is durable for about three weeks, about one month, about one and half months, about two months, about three months, about four months, about five months, or about six months.

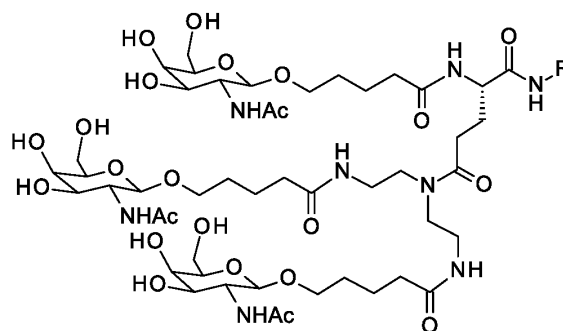
One of skill in the art recognizes that one or more mismatches may be present as
25 between the ANGPTL8 oligonucleotide, such as an antisense nucleotide disclosed herein, and the ANGPTL8 target nucleotide sequence and still function to regulate gene expression. In another embodiment, the oligonucleotide has 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, or 70 percent sequence identity with the target sequence or complementary to the target sequence. The

oligonucleotides may also have overhangs of 1-10, 1-5, or 1-3, or 3, 2, or 1 residue(s) at either the 5' or 3' end. The 5' or 3' ends may be further modified, for example with an abasic residue or a phosphate group.

The term "percent sequence identity" with respect to a reference nucleic acid
5 sequence is defined as the percentage of nucleotides, nucleosides, or nucleobases in a candidate sequence that are identical with the nucleotides, nucleosides, or nucleobases in the reference nucleic acid sequence, after optimally aligning the sequences and introducing gaps or overhangs, if necessary, to achieve the maximum percent sequence identity, using the
10 PID3 calculation, which is the number of identical nucleotide residues divided by the total number of nucleotides, nucleosides, or nucleobases of the shortest of the two sequences, multiplied by 100. See, e.g., Raghava, G., Barton, G.J. Quantification of the variation in percentage identity for protein sequence alignments. BMC Bioinformatics 7, 415 (2006). Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the
15 sequences being compared.

One of skill in the art recognizes that modifications of the RNAi agents (or compounds or RNAi molecules) comprising ANGPTL8 oligonucleotides, such as the sense strand or antisense strands of the RNAi agents disclosed herein, can increase its stability and half life. The modifications may be to the nucleotide or to the phosphodiester backbone, that
20 is the bonds between two nucleotide residues of the oligonucleotide, which is also termed an internucleotide linkage. For example, 2'-modifications on the sugar residue, suitably ribose, can increase its stability and half-life. These modifications include, but are not limited to, a 2' fluoro or 2' methoxy modification at the 2' OH group of an unmodified sugar. Backbone modifications, also termed modified internucleotide linkages herein, include a change from a
25 phosphodiester bond to a phosphorothioate (PS) bond.

Additional embodiments of the RNAi agents comprising a delivery moiety of Formula I comprise such nucleotide and internucleotide linkage modifications. Accordingly, in one embodiment is an RNAi agent comprising a delivery moiety of Formula I:



Formula I,

- 5 wherein R comprises a sense strand and an antisense strand,
 wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence
 selected from the group consisting of SEQ ID NOs: 405-525, and wherein the sense strand
 and the antisense strand form a region of complementarity of at least 15 nucleotides, and
 wherein the sense strand and antisense strand are each independently 18 to 23 nucleotides in
 10 length, and wherein the sense strand and antisense strand each independently comprise one or
 more modified nucleotides, and optionally wherein the sense strand and the antisense strand
 each independently comprise one or more modified internucleotide linkages, and wherein R
 is optionally conjugated to Formula I via a linker, and wherein the one or more modified
 nucleotides are independently 2' fluoro modified nucleotides or 2'-O-methyl modified
 15 nucleotides. In further embodiments, each nucleotide of the sense strand and each nucleotide
 of the antisense strand is a modified nucleotide. In other embodiments, the sense strand and
 antisense strand each independently comprise one or more modified internucleotide linkages.
 In further embodiments, each modified internucleotide linkage is a phosphorothioate linkage.
 In still further embodiments, the sense strand and antisense strand each independently
 20 comprise four phosphorothioate linkages. In further embodiments, the first two nucleotides
 at the 5' end of the sense strand and the last two nucleotides at the 3' end of the sense strand
 comprise phosphorothioate linkages, and the first two nucleotides at the 5' end of the

antisense strand and the last two nucleotides at the 3' end of the antisense strand comprise phosphorothioate linkages. In any of the embodiments of the RNAi agents disclosed herein, the 5' nucleotide of the antisense strand comprises a phosphate group or a phosphate analog.

As used herein, "oligonucleotide" (or "multimer" or "oligomer," used herein
5 interchangeably) as used herein, including the sense strands and antisense strands disclosed herein, means a chain of at least 10 nucleotide or nucleoside residues, and may comprise modified or unmodified bases, modified or unmodified sugars, and/or modified or unmodified bonds (also referred to herein interchangeably as the backbone or phosphodiester backbone or internucleotide linkage). The nucleotide residues may be connected by
10 phosphodiester bonds or modified bonds, also called phosphodiester internucleotide linkages or modified internucleotide linkages herein. The nucleotide residues may be modified at one or more atoms in the nucleobase pyrimidine or purine ring, or at one or more atoms in the sugar residue, or at one or more atoms of the bond between the ring-sugar and nucleobase. Modifications may also be made at the 5' or 3' end of the oligonucleotide strand and such
15 modified oligonucleotides or sense or antisense strands may referred to interchangeably as an oligonucleotide or sense or antisense strand herein, unless the context makes clear otherwise. Herein, nucleoside residues (i.e. nucleotides that lack one or more phosphate groups) may be referred to as modified nucleotides/nucleotide residues/nucleotide bases or simply nucleotides/nucleotide residues/nucleotide bases.

As used herein, "complementary" means a structural relationship between two
20 nucleotides (e.g., on two opposing nucleic acids or on opposing regions of a single nucleic acid strand, e.g., a hairpin) that would be expected to allow the two nucleotides to form base pairs with one another in the canonical Watson-Crick pairing. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an
25 opposing nucleic acid are complementary to each other. For example, they are predicted to base pair together by forming hydrogen bonds with one another. Likewise, two antiparallel nucleic acids may have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, such as the sense strands and antisense strands of the RNAi agents described herein.

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

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 or
10 substitutions of atoms other than hydrogen at the 2' position of the sugar, including modifications or substitutions in or of the nucleobase, sugar, or phosphate group.

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
15 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
20 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,
25 may have one or more mismatches, which may include internal mismatches or end mismatches.

As used herein, “duplex” and “duplex region” in reference to nucleic acids (e.g., oligonucleotides), means a double stranded nucleic acid structure formed through complementary base pairing of two antiparallel sequences of nucleotides, whether formed by

two covalently separate nucleic acid strands or by a single, folded strand (e.g., via a hairpin), and may be formed via annealing or hybridization under appropriate conditions.

As used herein, “linker” means a structure used to conjugate a nucleotide (e.g., oligonucleotide) to a delivery moiety. A linker can be “labile” or “cleavable” meaning a
5 linker that can be cleaved (e.g., by acidic pH). Likewise, a linker can be “stable” or “non-cleavable” meaning a linker that is not cleavable under physiological conditions.

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 internucleotide linkage can be a non-
10 naturally occurring linkage.

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
15 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.

As used herein, “nucleotide” means an organic compound having a nucleoside (a
20 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. A “nucleotide” can serve as a monomeric unit of nucleic acid polymers such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

As used herein, “overhang” means a terminal nucleotide(s) resulting from one strand
25 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.

As used herein, “phosphate analog” or “phosphate mimic” means a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some
5 embodiments, a phosphate analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate. 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
10 (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.,
15 Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash et al. (2015) Nuc. Acids Res. 43:2993-3011).

“Percent complementarity” is number of nucleotides, nucleosides, or nucleobases between two strands that exhibit the canonical pairing, divided by the total nucleotides, nucleosides, or nucleobases of the shortest of the two sequences, multiplied by 100.

20 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, also referred to as a modified nucleotide herein, is a ribonucleotide having one or more modifications or substitutions of atoms other than hydroxyl at the 2' position, including modifications or substitutions in or of the nucleobase, sugar, or phosphate group.

25 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).

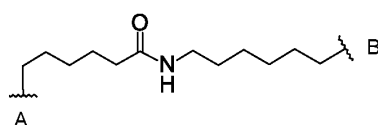
As used herein, “reduced expression,” and with respect to a gene (e.g., ANGPTL8) means a decrease in the amount or level of RNA transcript (e.g., ANGPTL8 mRNA) or

protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a sample, or a subject, when compared to an appropriate reference (e.g., a reference cell, population of cells, sample, or subject). For example, the act of contacting a cell with an oligonucleotide herein (e.g., an oligonucleotide having an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence including ANGPTL8 mRNA) may result in a decrease in the amount or level of mRNA, protein, and/or activity (e.g., via degradation of ANGPTL8 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., ANGPTL8). Specifically, and as used herein, “reduction of ANGPTL8 expression” means a decrease in the amount or level of ANGPTL8 mRNA, ANGPTL8 protein, and/or ANGPTL8 activity in a cell, a population of cells, a sample, or a subject when compared to an appropriate reference (e.g., a reference cell, population of cells, tissue, or subject).

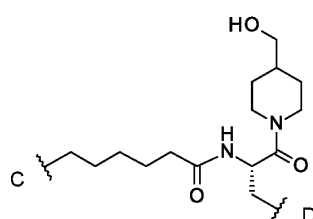
In certain embodiments the one or more oligonucleotides comprise a small interfering RNA (siRNA), miRNA (microRNA), short hairpin RNA (shRNA), single guide RNA (sgRNA), or antisense oligonucleotide (ASO). In a suitable embodiment, the one or more ANGPTL8 oligonucleotides comprises siRNA. In another suitable embodiment is an RNAi agent comprising a sense strand and antisense strand. In another suitable embodiment the one or more ANGPTL8 oligonucleotides is an siRNA comprising a sense strand and an antisense strand.

In some embodiments, the compound further comprises a linker, for example for conjugating one or more ANGPTL8 oligonucleotides, such as R, including wherein R comprises a sense strand and an antisense strand to Formula I. In other embodiments, the RNAi agent disclosed herein comprises a linker conjugating a double stranded oligonucleotide comprising a sense strand or an antisense strand. In other embodiments, the RNAi agent comprises a sense strand conjugated to the delivery moiety of Formula I via a linker. Suitable linkers are known in the art. In one embodiment, the linker comprises an alkyl chain, suitably C₁₋₈. In a further embodiment, the linker is an alkyl chain, suitably C₁₋₈.

In a further embodiment, the linker comprises Linker 1, as shown below (Formula II herein having connection points A and B). In a further embodiment, the linker is Linker 1. In another embodiment the linker comprises a piperidine ring. In a further suitable embodiment, the linker comprises Linker 2, as shown below (Formula III herein having connection points C and D). In a further suitable embodiment, the linker is Linker 2.



Linker 1 (Formula II)



Linker 2 (Formula III)

One of skill in the art will recognize that the linker may be on the 5' or 3' end of an ANGPTL8 oligonucleotide including R, including wherein R comprises a sense or antisense strand, of an RNAi agent herein, or attached to one of the internal nucleotides. One of skill in the art will also recognize that the linker maybe linked or conjugated to the 5' or 3' end of an ANGPTL8 oligonucleotide including a sense or antisense strand herein. One of skill in the art will also recognize that placement of a delivery moiety, such as the delivery moieties comprising Formula I, whether via a linker or not, on the 5' end an ANPTL8 oligonucleotide such as an antisense strand of an RNAi agent herein may need to overcome potential inefficient loading of Ago2 loading, or other hindrance of the RISC complex activity. For example, for a delivery moiety comprising Formula I linked or conjugated to the sense or antisense strand of an RNAi agent herein, such as an siRNA comprising a sense strand and an antisense strand, placement of the delivery moiety at the 5' end of the antisense strand

may create difficulties for Ago2 loading and prevent efficient knockdown. In a suitable embodiment, the one or more ANPTL8 oligonucleotides or RNAi agents comprise an siRNA comprising a sense strand and an antisense strand, and the delivery moiety comprising Formula I is present on the 3' end of the sense strand. In a further embodiment, the delivery moiety comprising Formula I is conjugated to the 3' end of the sense strand via a linker. In yet a further embodiment the linker comprises a ring structure, suitably a piperidine ring. In yet a further embodiment, the linker comprises Linker 1 (Formula II). In yet a further embodiment, the linker is Linker 2 (Formula III). In an embodiment Linker 1, connection point A, or Linker 2, connection point C, is conjugated to Formula I. In an embodiment Linker 1, connection point A, is conjugated to Formula I and connection point B is conjugated to R. In an embodiment Linker 2, connection point C, is conjugated to Formula I and connection point D is conjugated to R. In an embodiment Linker 1, connection point A, is conjugated to Formula I and connection point B is conjugated to a phosphate group which is conjugated to R. In an embodiment Linker 2, connection point C, is conjugated to Formula I and connection point D is conjugated to a phosphate group which is conjugated to R.

In certain embodiments, the ANPTL8 oligonucleotide such as an antisense strand is complementary to a sequence of Table 1, that is complementary to a sequence represented by any one of SEQ ID NO:3 to SEQ ID NO:123. In suitable embodiments, the ANPTL8 oligonucleotide is complementary to a sequence in Table 2, that is the sequence is complementary to a sequence represented by any one of SEQ ID NO:3, 6, 10, 11, 12, 13, 16, 18, 23, 24, 26, 27, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 46, 47, 49, 50, 52, 55, 56, 57, 61, 62, 63, 64, 65, 66, 67, 69, 70, 71, 72, 73, 74, 77, 88, 89, 90, 91, 93, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, or 107.

In further embodiments, the ANPTL8 oligonucleotide or RNAi agent herein comprises an siRNA comprising a sense strand and an antisense strand. In still further embodiments, the siRNA comprises a sense strand of Table 2, that is a sense strand comprising or having a sequence represented by any one of SEQ ID NO:124, 125, 126, 127,

128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145,
146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163,
164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181,
182, 183, 184, 185, 186, 187, 188, 189, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200,
5 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218,
219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, or 230. In other further embodiments
the ANPTL8 oligonucleotide or RNAi agent herein comprises an antisense strand of Table 2,
that is an antisense strand comprising or having a sequence represented by one of SEQ ID
NO:231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248,
10 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266,
267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284,
285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302,
303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320,
321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338,
15 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356,
357, 358, 359, or 360. In still further embodiments, the siRNA comprises a sense strand and
an antisense strand from one row of Table 11. In one of these further embodiments, the
siRNA comprises a sense strand and an antisense strand from row 1, that is the siRNA
comprises a sense strand comprising SEQ ID NO:124 and an antisense strand comprising
20 SEQ ID NO:231. In other further embodiments, the siRNA comprises a sense strand and an
antisense strand from row 2, that is the siRNA comprises a sense strand comprising SEQ ID
NO:125 and an antisense strand comprising SEQ ID NO:232. In other further embodiments
the siRNA comprises a sense strand and an antisense strand from the same row of Table 11,
wherein the row is selected from the group consisting of rows 1 to 174 of Table 11 (rows
25 labeled 1A to 174e5).

In further embodiments the sense strand and the antisense strand are modified. In
further embodiments the modification is on the nucleotide, the backbone, i.e. the
internucleoside linkage (phosphodiester bond), or both. In a further embodiment, the one or
more modified internucleotide linkage is a phosphorothioate (PS) bond. In other

embodiments, the internucleotide linkage is a modified internucleotide linkage that is a phosphorothioate (PS) bond. In further embodiments the modification is a 2' fluoro group or a 2' methoxy group on the ribose, or a PS bond, or both. In further embodiments, one or more of all three of these recited modifications are present. In further embodiments, the
5 siRNA comprises between one to ten 2' fluoro modifications on the ribose. In other embodiments the siRNA comprises between one to ten 2' fluoro modifications on the ribose and the remainder of the nucleotides, that is, the nucleotides that do not have a 2' fluoro modification, have a 2' methoxy group modification on the ribose.

In other embodiments of the compounds such as the RNAi agents disclosed herein,
10 the one or more oligonucleotides comprise an siRNA comprising a sense strand and an antisense strand. In a further embodiment, the sense strand and the antisense strand are each between 15-40 nucleotides in length. In suitable embodiments, the antisense strand is 23 nucleotides in length. In suitable embodiments, the sense strand is 21 nucleotides in length. In other suitable embodiments, the antisense strand is 23 nucleotides in length and the sense
15 strand is 21 nucleotides in length. In another embodiment, the sense strand and the antisense strand anneal, and optionally comprise one or more 5' or 3' nucleotide overhangs, one or more 5' or 3' blunt ends, or a combination of both.

In another embodiment of the RNAi molecules including the RNAi agents disclosed herein, the 5' or 3' ends of the ANGPTL8 oligonucleotides, such as those represented by R,
20 including wherein R comprises a sense strand and an antisense strand, are further modified. In a further embodiment, the 5' end of the antisense strand is optionally phosphorylated. In a further embodiment, the nucleotide at 5' end of the antisense strand comprises a 5' vinylphosphonate modification. In another embodiment, the nucleotide at the 5' end of the antisense strand comprises a phosphate group. In another embodiment, the nucleotide at the
25 5' end of the antisense strand comprises a phosphate analog.

In other embodiments the RNAi molecules such as the RNAi agents disclosed herein comprise an siRNA that comprises Formula I and a sense or antisense strand of Table 6 or 8. In other embodiments, the RNAi molecule or RNAi agent, each disclosed herein, comprises Formula I and a sense strand comprising a sequence of any one of SEQ ID NO:361, SEQ ID

NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, or SEQ ID NO:366. In other embodiments, the RNAi molecule or RNAi agent, each disclosed herein, comprises Formula I and an siRNA comprising an antisense strand comprising a sequence of any one of SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, or SEQ ID NO:372. In a further embodiment, the RNAi molecule or RNAi agent, each disclosed herein, comprises Formula I and an siRNA comprising a sense strand and an antisense strand selected from the pairs of sequences as set forth in a-f:

- a. SEQ ID NO:361 and SEQ ID NO:367;
- b. SEQ ID NO:362 and SEQ ID NO:368;
- 10 c. SEQ ID NO:363 and SEQ ID NO:369;
- d. SEQ ID NO:364 and SEQ ID NO:370;
- e. SEQ ID NO:365 and SEQ ID NO:371; or
- f. SEQ ID NO:366 and SEQ ID NO:372.

In still further embodiments, the RNAi molecules including the RNAi agent disclosed herein are conjugated to Formula I via a linker of Formula III (i.e. linker 2). In yet further embodiments, the linker of Formula III is conjugated to the nucleotide at the 3' end of the sense strand. In further embodiments, any 5' phosphate on the antisense strand is omitted, and one or more 2' fluoro residues in the ribose are removed. In a further embodiment, any 2' fluoro residues that are removed are replaced by 2' methoxy modifications at the same position.

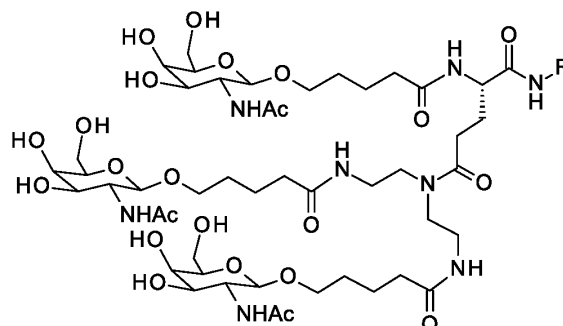
The RNAi molecules herein comprising Formula I and one or more ANGPTL8 oligonucleotides, such as those represented by R, including wherein R comprises a sense strand and an antisense strand, are useful in therapy, for diseases of the liver or involving adipose tissue. These are formulated into pharmaceutical compositions compatible for use in patients, suitably humans. The pharmaceutical compositions disclosed herein comprise one or more carriers, diluents, and excipients that are compatible with the RNAi molecules or RNAi agents herein and other components of the composition or formulation and not

deleterious to the patient. Examples of pharmaceutical compositions and processes for their preparation can be found in “Remington: The Science and Practice of Pharmacy”, Loyd, V., *et al.* Eds., 22nd Ed., Mack Publishing Co., 2012.

Accordingly, in one embodiment is a pharmaceutical composition comprising an
5 RNAi molecule or RNAi agent disclosed herein, comprising Formula I and one or more
ANGPTL8 oligonucleotides, such as those represented by R, including wherein R comprises
a sense strand and an antisense strand, and one or more pharmaceutically acceptable
excipients. In further embodiments the RNA molecule such as an RNAi molecule or RNAi
agent disclosed herein, and pharmaceutical compositions thereof, are for use in therapy or
10 treatment of disease.

Another embodiment is the RNAi molecules or RNAi agents comprising Formula I
and one or more ANGPTL8 oligonucleotides, such as those represented by R, including
wherein R comprises a sense strand and an antisense strand, or pharmaceutical compositions
thereof, for use in therapy. Another embodiment is an RNAi agent disclosed herein for use
15 in therapy. In a further embodiment, the therapy involves decreasing levels of ANGPTL8
expression, such as relative to an untreated or control or placebo therapy. A further
embodiment is wherein the therapy is for diseases of the liver or involving the liver. Another
embodiment is a method of treatment of a liver disease comprising administering an RNAi
molecule disclosed herein, suitably an RNAi molecule comprising Formula I and one or
20 more ANGPTL8 oligonucleotides including R, such as wherein R comprises a sense strand
and an antisense strand disclosed herein, suitably administered in an effective amount, or a
pharmaceutical composition of any of the preceding. Another embodiment is a method of
treating liver disease in a patient in need thereof comprising administering an RNAi agent
disclosed herein, suitably an effective amount thereof, or a pharmaceutical composition
25 comprising the RNAi agent and one or more pharmaceutically acceptable excipients.

Another embodiment is an RNA interference (RNAi) agent comprising Formula I:



Formula I,

and a sense strand and an antisense strand, wherein the antisense strand comprises at least 18
 5 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs:
 405-525, and wherein the sense strand and the antisense strand form a region of
 complementarity of at least 15 nucleotides, and wherein the sense strand and antisense strand
 are each independently 18 to 23 nucleotides in length, and optionally wherein the sense
 strand and antisense strand each independently comprise one or more modified nucleotides,
 10 and optionally wherein one or more internucleotide linkages of the sense strand and the
 antisense strand are modified internucleotide linkages, and wherein the sense or the antisense
 strand is conjugated to Formula I, optionally via a linker.

The oligonucleotides such as the sense and antisense strands disclosed herein, may also
 be conjugated to alternative delivery moieties, for targeting to the liver, or to other tissues to
 15 decrease expression of ANGPTL8. The oligonucleotides such as the sense and antisense
 strands disclosed herein, may also be unconjugated, and instead encapsulated or delivered by
 another means not requiring conjugation, to a tissue of interest to decrease expression of
 ANGPTL8.

Accordingly, other embodiments of the RNAi agents disclosed herein RNAi agents
 20 comprising a delivery moiety conjugated to R, optionally via a linker L, having a formula R-
 L-D, wherein R comprises an antisense or a sense strand or both, and wherein the antisense
 strand comprises at least 15 contiguous nucleotides of a sequence that is complementary to

the mRNA transcript of ANGPTL8, and wherein the sense strand and the antisense strand form a region of complementarity of at least 15 nucleotides, and wherein the sense strand and/or antisense strand, if and when present, are each independently 15 to 30 nucleotides in length, and optionally wherein the sense strand and antisense strand, if and when present, each independently comprise one or more modified nucleotides, and optionally wherein the sense strand and/or the antisense strand each independently comprise one or more modified internucleotide linkages. In another embodiment, the antisense strand comprises at least 15 contiguous nucleotides of a sequence that is complementary to SEQ ID NO:1. In a further embodiment, the sense strand and antisense strand are each independently 18 to 23 nucleotides in length. In a further embodiment of any of these RNAi agents, the antisense strand forms a region of complementarity of at least 18 nucleotides to the mRNA transcript of ANGPTL8. In a different further embodiment of any of these RNAi agents, the antisense strand forms a region of complementarity of at least 18 nucleotides to SEQ ID NO:1.

In a further embodiment is an RNAi agent wherein the antisense strand comprises at least 15 nucleotides of a sequence selected from the group consisting of SEQ ID NO:s 405-525. In yet a further embodiment, the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525.

In a further embodiment of the RNAi agents disclosed herein, the antisense strand comprises at least 15 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405, 408, 412, 413, 414, 415, 418, 420, 425, 426, 428, 429, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 448, 449, 451, 452, 454, 457, 458, 459, 463, 464, 465, 466, 467, 468, 469, 471, 472, 473, 474, 475, 476, 479, 490, 491, 492, 493, 495, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, and 509. In another embodiment, the antisense strand is selected from the group of antisense strand sequences in Table 2.

In another embodiment of the RNAi agents disclosed herein, the antisense strand is selected from the group consisting of SEQ ID NOs: 231-361, or a sequence having at least 90% sequence identity thereto. In other embodiments of the RNAi agents disclosed herein,

the sense strand is selected from the group consisting of SEQ ID NOs: 124-230, or a sequence having at least 90% sequence identity thereto.

In further embodiments of any of the RNAi agents described herein, the region of complementarity comprises 0, 1, 2, or 3 mismatches between the sense strand and the antisense strand.

In further embodiments of the RNAi agents, the sense strand and the antisense strand each independently comprise one or more modified nucleotides. In a further embodiment, the one or more modified nucleotides are independently 2' fluoro modified nucleotides or 2'-O-methyl modified nucleotides. In other embodiments, each nucleotide of the sense strand and each nucleotide of the antisense strand is a modified nucleotide, and in further embodiment, each of the modified nucleotides are independently a 2' fluoro modified nucleotide or a 2'-O-methyl modified nucleotide.

In other embodiments of the RNAi agents herein, the sense strand and antisense strand each independently comprise one or more modified internucleotide linkages. In a further embodiment, each modified internucleotide linkage is a phosphorothioate linkage. In other embodiments, the sense strand and antisense strand each independently comprise four phosphorothioate linkages. In further embodiments, the first two 5' nucleotides of the sense strand and the two terminal 3' nucleotides of the sense strand are phosphorothioate linkages. In further embodiments, the first two 5' nucleotides of the antisense strand and the two terminal 3' nucleotides of the antisense strand are phosphorothioate linkages.

In other embodiments of the RNAi agents herein, the 5' nucleotide of the antisense strand comprises a phosphate group or a phosphate analog.

A further embodiment of an RNAi agent disclosed herein is wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405, 408, 412, 413, 414, 415, 418, 420, 425, 426, 428, 429, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 448, 449, 451, 452, 454, 457, 458, 459, 463, 464, 465, 466, 467, 468, 469, 471, 472, 473, 474, 475, 476, 479, 490, 491, 492, 493, 495, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, and 509.

In another further embodiment, the RNAi agent comprises an antisense strand that is 23 nucleotides in length. In yet another further embodiment, the RNAi agent the sense strand is 21 nucleotides in length. In a suitable embodiment, the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length.

5 In another embodiment, the antisense strand of the RNAi agent is selected from the group consisting of SEQ ID NOs: 231-361, or a sequence having at least 90% sequence identity thereto. In another embodiment, the sense strand of the RNAi agent is selected from the group consisting of SEQ ID NOs: 124-230, or a sequence having at least 90% sequence identity thereto. The RNAi agent of any one of the preceding claims, wherein, in the region
10 of complementarity comprises 0, 1, 2, or 3 mismatches between the sense strand and the antisense strand.

In further embodiments, the RNAi agent comprises a sense strand or antisense strand comprising one or more modified nucleotides. In a further embodiment, the one or more modified nucleotides are independently a nucleotide having a 2' fluoro group or having a 2'
15 O-methyl group on the ribose. In a further embodiment, each nucleotide of the sense strand and the antisense strand is a modified nucleotide.

In another embodiment of the RNAi agents herein, each of the two nucleotides at the 5' and 3' end of each of the sense strand and the antisense strand have a modified internucleotide linkage. In a further embodiment, the modified internucleotide linkage, if
20 present, is a phosphorothiorate bond.

In another embodiment of the RNAi agents herein, the nucleotide at the 5' end of the antisense strand has a modification or a further modification that is a phosphate group or a phosphate analog.

In further embodiments of the RNAi agents herein, the antisense strand comprises a
25 sequence selected from the group consisting of SEQ ID NOs: 367-372, and 389-404, or a sequence having at least 90% sequence identity thereto.

In other further embodiments of the RNAi agents herein, the sense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 361-366 and 373-388, or a sequence having at least 90% sequence identity thereto.

5 In other further embodiments of the RNAi agents disclosed herein, the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- 10 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto;
- b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 90% sequence identity thereto;
- 15 c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 90% sequence identity thereto;
- d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 90% sequence identity thereto;
- 20 e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto;
- 25 f. a sense strand having the sequence set forth in SEQ ID NO:366, or a sequence having at least 90% sequence identity thereto, and the antisense strand having

- the sequence set forth in SEQ ID NO:372, or a sequence having at least 90% sequence identity thereto;
- 5 g. a sense strand having the sequence set forth in SEQ ID NO:373, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 90% sequence identity thereto;
- 10 h. a sense strand having the sequence set forth in SEQ ID NO:374, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO: 390 or a sequence having at least 90% sequence identity thereto;
- i. a sense strand having the sequence set forth in SEQ ID NO:375, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:391, or a sequence having at least 90% sequence identity thereto;
- 15 j. a sense strand having the sequence set forth in SEQ ID NO:376, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:392, or a sequence having at least 90% sequence identity thereto;
- 20 k. a sense strand having the sequence set forth in SEQ ID NO:377, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:393, or a sequence having at least 90% sequence identity thereto;
- 25 l. a sense strand having the sequence set forth in SEQ ID NO:378, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:394, or a sequence having at least 90% sequence identity thereto;
- m. a sense strand having the sequence set forth in SEQ ID NO:379, or a sequence having at least 90% sequence identity thereto, and an antisense strand having

- the sequence set forth in SEQ ID NO:395, or a sequence having at least 90% sequence identity thereto;
- 5 n. a sense strand having the sequence set forth in SEQ ID NO:380 or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 90% sequence identity thereto;
- 10 o. a sense strand having the sequence set forth in SEQ ID NO: 381, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 90% sequence identity thereto;
- 15 p. a sense strand having the sequence set forth in SEQ ID NO:382, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:397, or a sequence having at least 90% sequence identity thereto;
- 20 q. a sense strand having the sequence set forth in SEQ ID NO:383, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:398, or a sequence having at least 90% sequence identity thereto;
- r. a sense strand having the sequence set forth in SEQ ID NO:384, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:399, or a sequence having at least 90% sequence identity thereto;
- 25 s. a sense strand having the sequence set forth in SEQ ID NO:385, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:400, or a sequence having at least 90% sequence identity thereto;
- t. a sense strand having the sequence set forth in SEQ ID NO:386, or a sequence having at least 90% sequence identity thereto, and an antisense strand having

the sequence set forth in SEQ ID NO:401, or a sequence having at least 90% sequence identity thereto;

- 5 u. a sense strand having the sequence set forth in SEQ ID NO:387, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:402, or a sequence having at least 90% sequence identity thereto;
- v. a sense strand having the sequence set forth in SEQ ID NO:388, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:403, or a sequence having at least 90% sequence identity thereto; and
- 10 w. a sense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:404, or a sequence having at least 90% sequence identity thereto;

15 Suitably, the RNAi agents having the pair of recited oligonucleotide sequences comprise Formula I. In further suitable embodiments, the RNAi agents comprise Formula I conjugated to the nucleotide at the 3' end of the sense strand. In yet further embodiments, Formula I is conjugated to the nucleotide at the 3' end of the sense strand via a linker. In further embodiments, the linker is a linker of Formula III.

20 In other embodiments of the RNAi agents herein, the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto;
- 25 b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 95% sequence identity thereto;

- c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 95% sequence identity thereto;
- 5 d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 95% sequence identity thereto;
- e. a sense strand having the sequence set forth in SEQ ID NO:365, or a
10 sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto;
- f. a sense strand having the sequence set forth in SEQ ID NO:366, or a
15 sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:372, or a sequence having at least 95% sequence identity thereto;
- g. a sense strand having the sequence set forth in SEQ ID NO:373, or a
sequence having at least 95% sequence identity thereto, and the antisense
20 strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 95% sequence identity thereto;
- h. a sense strand having the sequence set forth in SEQ ID NO:374, or a
sequence having at least 95% sequence identity thereto, and an antisense
strand having the sequence set forth in SEQ ID NO: 390 or a sequence
having at least 95% sequence identity thereto;
- 25 i. a sense strand having the sequence set forth in SEQ ID NO:375, or a
sequence having at least 95% sequence identity thereto, and an antisense
strand having the sequence set forth in SEQ ID NO:391, or a sequence
having at least 95% sequence identity thereto;

- j. a sense strand having the sequence set forth in SEQ ID NO:376, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:392, or a sequence having at least 95% sequence identity thereto;
- 5 k. a sense strand having the sequence set forth in SEQ ID NO:377, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:393, or a sequence having at least 95% sequence identity thereto;
- 10 l. a sense strand having the sequence set forth in SEQ ID NO:378, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:394, or a sequence having at least 95% sequence identity thereto;
- 15 m. a sense strand having the sequence set forth in SEQ ID NO:379, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:395, or a sequence having at least 95% sequence identity thereto;
- 20 n. a sense strand having the sequence set forth in SEQ ID NO:380, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 95% sequence identity thereto;
- 25 o. a sense strand having the sequence set forth in SEQ ID NO: 381, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 95% sequence identity thereto;
- p. a sense strand having the sequence set forth in SEQ ID NO:382, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:397, or a sequence having at least 95% sequence identity thereto;

- q. a sense strand having the sequence set forth in SEQ ID NO:383, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:398, or a sequence having at least 95% sequence identity thereto;
- 5 r. a sense strand having the sequence set forth in SEQ ID NO:384, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:399, or a sequence having at least 95% sequence identity thereto;
- 10 s. a sense strand having the sequence set forth in SEQ ID NO:385, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:400, or a sequence having at least 95% sequence identity thereto;
- 15 t. a sense strand having the sequence set forth in SEQ ID NO:386, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:401, or a sequence having at least 95% sequence identity thereto;
- 20 u. a sense strand having the sequence set forth in SEQ ID NO:387, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:402, or a sequence having at least 95% sequence identity thereto;
- v. a sense strand having the sequence set forth in SEQ ID NO:388, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:403, or a sequence having at least 95% sequence identity thereto; and
- 25 w. a sense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:404, or a sequence having at least 95% sequence identity thereto;

Suitably, the RNAi agents having the pair of recited oligonucleotide sequences comprise Formula I. In further suitable embodiments, the RNAi agents comprise Formula I conjugated to the nucleotide at the 3' end of the sense strand. In yet further embodiments, Formula I is conjugated to the nucleotide at the 3' end of the sense strand via a linker. In further
5 embodiments, the linker is a linker of Formula III.

In other embodiments of the RNAi agents disclosed herein, the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- 10 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto;
- 15 b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 90% sequence identity thereto;
- 20 c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 90% sequence identity thereto;
- 25 d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 90% sequence identity thereto; and
- e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto;

Suitably, the RNAi agents having the pair of recited oligonucleotide sequences comprise Formula I. In further suitable embodiments, the RNAi agents comprise Formula I conjugated to the nucleotide at the 3' end of the sense strand. In yet further embodiments, Formula I is conjugated to the nucleotide at the 3' end of the sense strand via a linker. In
5 further embodiments, the linker is a linker of Formula III.

In a further embodiment of the RNAi agents disclosed herein, the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- 10 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto;
- 15 b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 95% sequence identity thereto;
- 20 c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 95% sequence identity thereto;
- d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 95% sequence identity thereto; and
- 25 e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto.

Suitably, the RNAi agents having the pair of recited oligonucleotide sequences comprise Formula I. In further suitable embodiments, the RNAi agents comprise Formula I conjugated to the nucleotide at the 3' end of the sense strand. In yet further embodiments, Formula I is conjugated to the nucleotide at the 3' end of the sense strand via a linker. In further
5 embodiments, the linker is a linker of Formula III.

In another embodiment of the RNAi agents disclosed herein, is an RNA agent wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- 10 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto; and
- 15 b. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto.

Suitably, the RNAi agents having the pair of recited oligonucleotide sequences comprise Formula I. In further suitable embodiments, the RNAi agents comprise Formula I conjugated to the nucleotide at the 3' end of the sense strand. In yet further embodiments, Formula I is
20 conjugated to the nucleotide at the 3' end of the sense strand via a linker. In further embodiments, the linker is a linker of Formula III.

In other embodiments of the RNAi agents disclosed herein, the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- 25 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto; and

- b. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto.

- 5 Suitably, the RNAi agents having the pair of recited oligonucleotide sequences comprise Formula I. In further suitable embodiments, the RNAi agents comprise Formula I conjugated to the nucleotide at the 3' end of the sense strand. In yet further embodiments, Formula I is conjugated to the nucleotide at the 3' end of the sense strand via a linker. In further
embodiments, the linker is a linker of Formula III.
- 10 In other embodiments herein, the RNAi agent is capable of decreasing expression of the ANGPTL8 gene in a liver cell.
- In other embodiments, the RNAi agent disclosed herein is provided for use in therapy. Another embodiment is an RNAi molecule or RNAi agent disclosed herein, suitably comprising Formula I and one or more ANGPTL8 oligonucleotides including R, such as
- 15 wherein R comprises a sense strand and/or an antisense strand disclosed herein, or a pharmaceutical composition thereof, for use in the manufacture of a medicament, suitably for the treatment of liver disease or a disease involving the liver, each including dyslipidemia, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). In another
embodiment is the use of an RNAi molecule or RNAi agent disclosed herein, suitably
- 20 comprising Formula I and one or more ANGPTL8 oligonucleotides, including R, such as wherein R comprises a sense strand and/or an antisense strand disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament, suitably for the
treatment of liver disease or a disease involving the liver, each including dyslipidemia, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). In a further
- 25 embodiment, the NAFLD is non-alcoholic steatohepatitis (NASH). Another embodiment is an RNAi agent disclosed herein, or a pharmaceutical composition thereof, for use in the
manufacture of a medicament, suitably for the treatment of liver disease or a disease
involving the liver, each including dyslipidemia, cardiovascular disease, and non-alcoholic

fatty liver disease (NAFLD). In a further embodiment, the NAFLD is non-alcoholic steatohepatitis (NASH).

In other embodiments are methods of treating dyslipidemia comprising administering an effective amount of an RNAi molecule disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof. Another embodiment is an RNAi molecule disclosed
5 herein, or a pharmaceutical composition thereof, for use in treating dyslipidemia. In other embodiments are methods of treating dyslipidemia comprising administering an effective amount of an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof. Another embodiment is an RNAi agent disclosed herein, or a
10 pharmaceutical composition thereof, for use in treating dyslipidemia.

In other embodiments are provided methods of treating cardiovascular disease comprising administering an effective amount of the RNAi molecule disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof. Another embodiment is an RNAi molecule disclosed herein, or a pharmaceutical composition thereof, for use in treating
15 cardiovascular disease, optionally and suitably as measured by a decrease in hospitalizations and/or cardiovascular events and/or risk of either or both. In other embodiments are provided methods of treating cardiovascular disease comprising administering an effective amount of an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof. Another embodiment is an RNAi agent disclosed herein, or a
20 pharmaceutical composition thereof, for use in treating cardiovascular disease, optionally and suitably as measured by a decrease in hospitalizations and/or cardiovascular events and/or risk of either or both.

In other embodiments are methods preventing a cardiovascular event, comprising administering an effective amount of an RNAi molecule disclosed herein or a pharmaceutical
25 composition thereof, to a patient in need thereof. In other embodiments are methods preventing a cardiovascular event, comprising administering an effective amount of an RNAi agent disclosed herein or a pharmaceutical composition thereof, to a patient in need thereof. In further embodiments the cardiovascular event is myocardial infarction.

In other embodiments are methods of decreasing hospitalizations related to cardiovascular disease or events comprising administering an effective amount of an RNAi molecule disclosed herein, such as an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof.

5 In other embodiments are methods of treating non-alcoholic fatty liver disease (NAFLD) comprising administering an effective amount of an RNAi molecule such as an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof. Another embodiment is an RNAi molecule such as an RNAi agent disclosed herein, or a pharmaceutical composition thereof, for use in treating NAFLD. In further
10 embodiments, the NAFLD is NASH.

In other embodiments are methods of lowering triglyceride levels, comprising administering an effective amount of an RNAi molecule such as an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof.

15 In other embodiments are methods of inhibiting lipoprotein lipase (LPL) comprising administering an effective amount of an RNAi molecule such as an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need thereof.

In other embodiments are methods of increasing catabolism of triglyceride rich lipoproteins comprising administering an effective amount of an RNAi molecule such as an RNAi agent disclosed herein, or a pharmaceutical composition thereof, to a patient in need
20 thereof.

In other embodiments are methods of treating liver disease in a patient that would benefit from decreasing expression levels of ANGPTL8, comprising administering an effective amount of an RNAi molecule such as an RNAi agent disclosed herein or a pharmaceutical composition thereof, to a patient in need thereof.

25 As used herein, the term “effective amount” refers to an amount that is effective in treating a disorder or disease.

As used herein, the term “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.

5 The RNAi agents are further described in the nonlimiting examples herein.

EXAMPLE 1

Table 1. Target and antisense sequences for designed siRNAs

SEQ ID NO (DNA SEQ)	Start Position on DNA	End Position on DNA	18mer Target DNA Sequence (5'-3')	SEQ ID NO (RNA SEQ)	18 mer Antisense RNA sequence (5'-3')
3	120	137	AGCTGACCCTGCTCTTCC	405	GGAAGAGCAGGGUCAGCU
4	141	158	GGACCCTGCAGCTGGGCC	406	GGCCAGCUGCAGGGUCC
5	150	167	AGCTGGGCCAGGCCCTCA	407	UGAGGGCCUGGCCAGCU
6	185	202	ACGGAGGGACGGCTGACA	408	UGUCAGCCGUCCUCCGU
7	186	203	CGGAGGGACGGCTGACAA	409	UUGUCAGCCGUCCUCCG
8	191	208	GGACGGCTGACAAAGGCC	410	GGCCUUUGUCAGCCGUCC
9	194	211	CGGCTGACAAAGGCCAGG	411	CCUGGCCUUUGUCAGCCG
10	195	212	GGCTGACAAAGGCCAGGA	412	UCCUGGCCUUUGUCAGCC
11	197	214	CTGACAAAGGCCAGGAAC	413	GUUCCUGGCCUUUGUCAG
12	210	227	GGAACAGCCTGGGTCTCT	414	AGAGACCCAGGCUGUUC
13	211	228	GAACAGCCTGGGTCTCTA	415	UAGAGACCCAGGCUGUUC
14	215	232	AGCCTGGGTCTCTATGGC	416	GCCAUAGAGACCCAGGCU
15	217	234	CCTGGGTCTCTATGGCCG	417	CGGCCAUAGAGACCCAGG
16	218	235	CTGGGTCTCTATGGCCGC	418	GCGGCCAUAGAGACCCAG
17	219	236	TGGGTCTCTATGGCCGCA	419	UGCGGCCAUAGAGACCCA
18	220	237	GGGTCTCTATGGCCGCAC	420	GUGCGGCCAUAGAGACCC
19	259	276	GGTCAGCCGGGGCCGGGA	421	UCCCGGCCCCGGCUGACC
20	267	284	GGGGCCGGGATGCAGCCC	422	GGGUGCAUCCCGGCCCC
21	270	287	GCCGGGATGCAGCCCAGG	423	CCUGGGCUGCAUCCCGGC
22	271	288	CCGGGATGCAGCCCAGGA	424	UCCUGGGCUGCAUCCCGG
23	273	290	GGGATGCAGCCCAGGAAC	425	GUUCCUGGGCUGCAUCCC
24	274	291	GGATGCAGCCCAGGAACT	426	AGUUCCUGGGCUGCAUCC
25	281	298	GCCCAGGAACTTCGGGCA	427	UGCCCGAAGUCCUGGGC
26	282	299	CCCAGGAACTTCGGGCAA	428	UUGCCCGAAGUCCUGGG
27	283	300	CCAGGAACTTCGGGCAAG	429	CUUGCCCGAAGUCCUGG

28	284	301	CAGGAACTTCGGGCAAGC	430	GCUUGCCCCGAAGUCCUG
29	285	302	AGGAACTTCGGGCAAGCC	431	GGCUUGCCCCGAAGUCCU
30	286	303	GGAAGCTTCGGGCAAGCCT	432	AGGCUUGCCCCGAAGUCC
31	287	304	GAAGCTTCGGGCAAGCCTG	433	CAGGCUUGCCCCGAAGUUC
32	290	307	CTTCGGGCAAGCCTGTTG	434	CAACAGGCUUGCCCCGAAG
33	291	308	TTCGGGCAAGCCTGTTGG	435	CCAACAGGCUUGCCCCGAA
34	293	310	CGGGCAAGCCTGTTGGAG	436	CUCCAACAGGCUUGCCCCG
35	297	314	CAAGCCTGTTGGAGACTC	437	GAGUCUCCAACAGGCUUG
36	299	316	AGCCTGTTGGAGACTCAG	438	CUGAGUCUCCAACAGGCU
37	300	317	GCCTGTTGGAGACTCAGA	439	UCUGAGUCUCCAACAGGC
38	303	320	TGTTGGAGACTCAGATGG	440	CCAUCUGAGUCUCCAACA
39	304	321	GTTGGAGACTCAGATGGA	441	UCCAUCUGAGUCUCCAAC
40	309	326	AGACTCAGATGGAGGAGG	442	CCUCCUCCAUCUGAGUCU
41	310	327	GACTCAGATGGAGGAGGA	443	UCCUCCUCCAUCUGAGUC
42	311	328	ACTCAGATGGAGGAGGAT	444	AUCCUCCUCCAUCUGAGU
43	312	329	CTCAGATGGAGGAGGATA	445	UAUCCUCCUCCAUCUGAG
44	313	330	TCAGATGGAGGAGGATAT	446	AUAUCCUCCUCCAUCUGA
45	314	331	CAGATGGAGGAGGATATT	447	AAUAUCCUCCUCCAUCUG
46	315	332	AGATGGAGGAGGATATTC	448	GAAUAUCCUCCUCCAUCU
47	316	333	GATGGAGGAGGATATTCT	449	AGAAUAUCCUCCUCCAUC
48	317	334	ATGGAGGAGGATATTCTG	450	CAGAAUAUCCUCCUCCAUC
49	319	336	GGAGGAGGATATTCTGCA	451	UGCAGAAUAUCCUCCUCC
50	321	338	AGGAGGATATTCTGCAGC	452	GCUGCAGAAUAUCCUCCU
51	372	389	AGGTGGCCCAGGCACAGA	453	UCUGUGCCUGGGCCACCU
52	379	396	CCAGGCACAGAAGGTGCT	454	AGCACCUUCUGUGCCUGG
53	411	428	AGCGGCTAGAAGTCCAGC	455	GCUGGACUUCUAGCCGCU
54	412	429	GCGGCTAGAAGTCCAGCT	456	AGCUGGACUUCUAGCCGC
55	413	430	CGGCTAGAAGTCCAGCTG	457	CAGCUGGACUUCUAGCCG
56	414	431	GGCTAGAAGTCCAGCTGA	458	UCAGCUGGACUUCUAGCC
57	415	432	GCTAGAAGTCCAGCTGAG	459	CUCAGCUGGACUUCUAGC
58	420	437	AAGTCCAGCTGAGGAGCG	460	CGCUCCUCAGCUGGACUU
59	421	438	AGTCCAGCTGAGGAGCGC	461	GCGCUCCUCAGCUGGACU
60	438	455	CCTGGCTGGGCCCTGCCT	462	AGGCAGGGCCCAGCCAGG
61	459	476	GAGAATTTGAGGTCTTAA	463	UUAAGACCUCAAAUCUC
62	460	477	AGAATTTGAGGTCTTAAA	464	UUUAAGACCUCAAAUCU
63	462	479	AATTTGAGGTCTTAAAGG	465	CCUUUAAGACCUCAAAUC
64	463	480	ATTTGAGGTCTTAAAGGC	466	GCCUUUAAGACCUCAAAUC
65	464	481	TTTGAGGTCTTAAAGGCT	467	AGCCUUUAAGACCUCAAA

66	465	482	TTGAGGTCTTAAAGGCTC	468	GAGCCUUUAAGACCUCAA
67	466	483	TGAGGTCTTAAAGGCTCA	469	UGAGCCUUUAAGACCUCA
68	467	484	GAGGTCTTAAAGGCTCAC	470	GUGAGCCUUUAAGACCUC
69	469	486	GGTCTTAAAGGCTCACGC	471	GCGUGAGCCUUUAAGACC
70	471	488	TCTTAAAGGCTCACGCTG	472	CAGCGUGAGCCUUUAAGA
71	472	489	CTTAAAGGCTCACGCTGA	473	UCAGCGUGAGCCUUUAAG
72	473	490	TTAAAGGCTCACGCTGAC	474	GUCAGCGUGAGCCUUUAA
73	474	491	TAAAGGCTCACGCTGACA	475	UGUCAGCGUGAGCCUUUA
74	475	492	AAAGGCTCACGCTGACAA	476	UUGUCAGCGUGAGCCUUU
75	476	493	AAGGCTCACGCTGACAAG	477	CUUGUCAGCGUGAGCCUU
76	477	494	AGGCTCACGCTGACAAGC	478	GCUUGUCAGCGUGAGCCU
77	479	496	GCTCACGCTGACAAGCAG	479	CUGCUUGUCAGCGUGAGC
78	480	497	CTCACGCTGACAAGCAGA	480	UCUGCUUGUCAGCGUGAG
79	481	498	TCACGCTGACAAGCAGAG	481	CUCUGCUUGUCAGCGUGA
80	482	499	CACGCTGACAAGCAGAGC	482	GCUCUGCUUGUCAGCGUG
81	483	500	ACGCTGACAAGCAGAGCC	483	GGCUCUGCUUGUCAGCGU
82	485	502	GCTGACAAGCAGAGCCAC	484	GUGGCUUGCUUGUCAGC
83	513	530	CCCTCACAGGCCACGTGC	485	GCACGUGGCCUGUGAGGG
84	514	531	CCTCACAGGCCACGTGCA	486	UGCACGUGGCCUGUGAGG
85	520	537	AGGCCACGTGCAGCGGCA	487	UGCCGCUGCACGUGGCCU
86	521	538	GGCCACGTGCAGCGGCAG	488	CUGCCGCUGCACGUGGCC
87	524	541	CACGTGCAGCGGCAGAGG	489	CCUCUGCCGCUGCACGUG
88	530	547	CAGCGGCAGAGGCGGGAG	490	CUCCCGCCUCUGCCGCUG
89	534	551	GGCAGAGGCGGGAGATGG	491	CCAUCUCCCGCCUCUGCC
90	540	557	GGCGGGAGATGGTGGCAC	492	GUGCCACCAUCUCCCGCC
91	543	560	GGGAGATGGTGGCACAGC	493	GCUGUGCCACCAUCUCCC
92	546	563	AGATGGTGGCACAGCAGC	494	GCUGCUGUGCCACCAUCU
93	553	570	GGCACAGCAGCATCGGCT	495	AGCCGAUGCUGCUGUGCC
94	555	572	CACAGCAGCATCGGCTGC	496	GCAGCCGAUGCUGCUGUG
95	557	574	CAGCAGCATCGGCTGCGA	497	UCGCAGCCGAUGCUGCUG
96	558	575	AGCAGCATCGGCTGCGAC	498	GUCGCAGCCGAUGCUGCU
97	559	576	GCAGCATCGGCTGCGACA	499	UGUCGCAGCCGAUGCUGC
98	560	577	CAGCATCGGCTGCGACAG	500	CUGUCGCAGCCGAUGCUG
99	561	578	AGCATCGGCTGCGACAGA	501	UCUGUCGCAGCCGAUGCU
100	562	579	GCATCGGCTGCGACAGAT	502	AUCUGUCGCAGCCGAUGC
101	563	580	CATCGGCTGCGACAGATC	503	GAUCUGUCGCAGCCGAUG
102	564	581	ATCGGCTGCGACAGATCC	504	GGAUCUGUCGCAGCCGAU
103	565	582	TCGGCTGCGACAGATCCA	505	UGGAUCUGUCGCAGCCGA

104	567	584	GGCTGCGACAGATCCAGG	506	CCUGGAUCUGUCGCAGCC
105	569	586	CTGCGACAGATCCAGGAG	507	CUCCUGGAUCUGUCGAG
106	570	587	TGCGACAGATCCAGGAGA	508	UCUCCUGGAUCUGUCGCA
107	571	588	GCGACAGATCCAGGAGAG	509	CUCUCCUGGAUCUGUCGC
108	607	624	CCCAGCCTGAATCTGCCT	510	AGGCAGAUUCAGGCUGGG
109	610	627	AGCCTGAATCTGCCTGGA	511	UCCAGGCAGAUUCAGGCU
110	611	628	GCCTGAATCTGCCTGGAT	512	AUCCAGGCAGAUUCAGGC
111	619	636	CTGCCTGGATGGAACCTGA	513	UCAGUCCAUCCAGGCAG
112	644	661	TCATGCTGCAAGGAACAC	514	GUGUCCUUGCAGCAUGA
113	652	669	CAAGGAACACTTCCACGC	515	GCGUGGAAGUGUCCUUG
114	655	672	GGAACACTTCCACGCCCC	516	GGGCGUGGAAGUGUCC
115	698	715	TGCCTGTTCACCTGGGATC	517	GAUCCAGUGAACAGGCA
116	699	716	GCCTGTTCACCTGGGATCA	518	UGAUCCAGUGAACAGGC
117	701	718	CTGTTCACCTGGGATCAGC	519	GCUGAUCCAGUGAACAG
118	702	719	TGTTCACTGGGATCAGCC	520	GGCUGAUCCAGUGAACAA
119	709	726	TGGGATCAGCCAGGGCGC	521	GCGCCCUGGCUGAUCCCA
120	710	727	GGGATCAGCCAGGGCGCC	522	GGGCCCUGGCUGAUCCC
121	847	864	CATTAAAGCAGAGTCGTG	523	CACGACUCUGCUUUAUG
122	848	865	ATTAAAGCAGAGTCGTGG	524	CCACGACUCUGCUUUAU
123	850	867	TAAAGCAGAGTCGTGGCA	525	UGCCACGACUCUGCUUUA

siRNAs are designed that are complementary to the 18mer regions of the ANGPTL8 transcript NM_(SEQ ID NO: 1) as shown above in Table 1. The sense strand and the antisense RNA oligonucleotides strands are between 18 and 23 nucleotides in length, with optional overhangs of 1 to 5 ribonucleotides, with 1-10 fluoro additions at the 2' position of ribose, and the remaining residues are methylated at the 2' position of ribose (creating an 2' methoxy i.e. a 2' O-methyl modification). Some antisense strands are phosphorylated at the 5' position. Each siRNA is conjugated to a delivery moiety comprising 3 GalNAc group; select delivery moieties comprise Formula I while others comprise a control moiety. One or more phosphodiester bonds are present at the 5' and 3' ends.

Knockdown of ANGPTL8 expression by these siRNAs is assayed using the following procedure: mouse primary hepatocytes (MPH) are freshly isolated from an AAV-ANGPTL8 humanized mouse, added to Corning plates at 15k per well, and siRNA are added directly to the well. For single measurements, 1 uM (1000 nM) is used; to generate concentration/dose

response curves final concentrations of 1000, 333, 111, 37, 12, 4, 1.37, 0.46, 0.15, 0.05, and 0.017 nM of GalNAc-conjugated siRNA concentration is used.

Treated cells are lysed and RNA is isolated using the Quick-RNA 96 Kit (Zymo Research) directly into the 96 well plate. The eluted RNA is used immediately or stored frozen. cDNA is synthesized using Fast Advanced RT Master Mix (Invitrogen) and using the following steps in a thermocycler: 37C for 30 minutes, 95C for 5 minutes, and 4C hold. Polymerase Chain Reaction (PCR) is performed via TaqMan RT PCR (Life Technologies) using the following cycles temperatures and times: 50C for 2 minutes, 95C for 10 minutes, 40 cycles of 95C for 15 seconds and 60C for 1 minute.

The human ANGPTL8 levels are normalized to mouse Rplp0 (Life Technologies) and represent the relative knockdown of human ANGPTL8 mRNA expression as compared to vehicle-treated control cells. IC50 values are calculated using a 4-parameter fit model using XLFit.

The ANGPTL8 target regions of siRNAs that exhibited a greater than 50% knockdown are shown below in Table 2.

Table 2.

SEQ ID NO (DNA SEQ)	Start Position on DNA	End Position on DNA	18mer DNA Sequence (5'-3')	SEQ ID NO (RNA SEQ)	Antisense RNA sequence (5' - 3')
3	120	137	AGCTGACCCTGCTCTTCC	405	GGAAGAGCAGGGUCAGCU
6	185	202	ACGGAGGGACGGCTGACA	408	UGUCAGCCGUCCUCCGU
10	195	212	GGCTGACAAAGGCCAGGA	412	UCCUGGCCUUUGUCAGCC
11	197	214	CTGACAAAGGCCAGGAAC	413	GUUCCUGGCCUUUGUCAG
12	210	227	GGAACAGCCTGGGTCTCT	414	AGAGACCCAGGCUGUUC
13	211	228	GAACAGCCTGGGTCTCTA	415	UAGAGACCCAGGCUGUUC
16	218	235	CTGGGTCTCTATGGCCGC	418	GCGGCCAUAGAGACCCAG
18	220	237	GGGTCTCTATGGCCGCAC	420	GUGCGGCCAUAGAGACCC
23	273	290	GGGATGCAGCCCAGGAAC	425	GUUCCUGGGCUGCAUCCC
24	274	291	GGATGCAGCCCAGGAAC	426	AGUCCUGGGCUGCAUCC
26	282	299	CCCAGGAACCTCGGGCAA	428	UUGCCCGAAGUCCUGGG
27	283	300	CCAGGAACCTCGGGCAAG	429	CUUGCCCGAAGUCCUGG

30	286	303	GGAACCTTCGGGCAAGCCT	432	AGGCUUGCCCCGAAGUUC
31	287	304	GAACCTTCGGGCAAGCCTG	433	CAGGCUUGCCCCGAAGUUC
32	290	307	CTTCGGGCAAGCCTGTTG	434	CAACAGGCUUGCCCCGAAG
33	291	308	TTCGGGCAAGCCTGTTGG	435	CCAACAGGCUUGCCCCGAA
34	293	310	CGGGCAAGCCTGTTGGAG	436	CUCCAACAGGCUUGCCCCG
35	297	314	CAAGCCTGTTGGAGACTC	437	GAGUCUCCAACAGGCUUG
36	299	316	AGCCTGTTGGAGACTCAG	438	CUGAGUCUCCAACAGGCU
37	300	317	GCCTGTTGGAGACTCAGA	439	UCUGAGUCUCCAACAGGC
38	303	320	TGTTGGAGACTCAGATGG	440	CCAUCUGAGUCUCCAACA
39	304	321	GTTGGAGACTCAGATGGA	441	UCCAUCUGAGUCUCCAAC
40	309	326	AGACTCAGATGGAGGAGG	442	CCUCCUCCAUCUGAGUCU
41	310	327	GACTCAGATGGAGGAGGA	443	UCCUCCUCCAUCUGAGUC
42	311	328	ACTCAGATGGAGGAGGAT	444	AUCCUCCUCCAUCUGAGU
43	312	329	CTCAGATGGAGGAGGATA	445	UAUCCUCCUCCAUCUGAG
44	313	330	TCAGATGGAGGAGGATAT	446	AUAUCCUCCUCCAUCUGA
46	315	332	AGATGGAGGAGGATATTC	448	GAAUAUCCUCCUCCAUCU
47	316	333	GATGGAGGAGGATATTCT	449	AGAAUAUCCUCCUCCAUC
49	319	336	GGAGGAGGATATTCTGCA	451	UGCAGAAUAUCCUCCUCC
50	321	338	AGGAGGATATTCTGCAGC	452	GCUGCAGAAUAUCCUCCU
52	379	396	CCAGGCACAGAAGGTGCT	454	AGCACCUUCUGUGCCUGG
55	413	430	CGGCTAGAAGTCCAGCTG	457	CAGCUGGACUUCUAGCCG
56	414	431	GGCTAGAAGTCCAGCTGA	458	UCAGCUGGACUUCUAGCC
57	415	432	GCTAGAAGTCCAGCTGAG	459	CUCAGCUGGACUUCUAGC
61	459	476	GAGAATTTGAGGTCTTAA	463	UUAAGACCUCAAAUCUC
62	460	477	AGAATTTGAGGTCTTAAA	464	UUUAAGACCUCAAAUCU
63	462	479	AATTTGAGGTCTTAAAGG	465	CCUUUAAGACCUCAAAUC
64	463	480	ATTTGAGGTCTTAAAGGC	466	GCCUUUAAGACCUCAAAUC
65	464	481	TTTGAGGTCTTAAAGGCT	467	AGCCUUUAAGACCUCAAA
66	465	482	TTGAGGTCTTAAAGGCTC	468	GAGCCUUUAAGACCUCAA
67	466	483	TGAGGTCTTAAAGGCTCA	469	UGAGCCUUUAAGACCUC
69	469	486	GGTCTTAAAGGCTCACGC	471	GCGUGAGCCUUUAAGACC
70	471	488	TCTTAAAGGCTCACGCTG	472	CAGCGUGAGCCUUUAAGA
71	472	489	CTTAAAGGCTCACGCTGA	473	UCAGCGUGAGCCUUUAAG
72	473	490	TTAAAGGCTCACGCTGAC	474	GUCAGCGUGAGCCUUUA
73	474	491	TAAAGGCTCACGCTGACA	475	UGUCAGCGUGAGCCUUUA
74	475	492	AAAGGCTCACGCTGACAA	476	UUGUCAGCGUGAGCCUUU
77	479	496	GCTCACGCTGACAAGCAG	479	CUGCUUGUCAGCGUGAGC
88	530	547	CAGCGGCAGAGGCGGGAG	490	CUCCCGCCUCUGCCGCUG

89	534	551	GGCAGAGGCGGGAGATGG	491	CCAUCUCCCGCCUCUGCC
90	540	557	GGCGGGAGATGGTGGCAC	492	GUGCCACCAUCUCCCGCC
91	543	560	GGGAGATGGTGGCACAGC	493	GCUGUGCCACCAUCUCC
93	553	570	GGCACAGCAGCATCGGCT	495	AGCCGAUGCUGCUGUGCC
97	559	576	GCAGCATCGGCTGCGACA	499	UGUCGCAGCCGAUGCUGC
98	560	577	CAGCATCGGCTGCGACAG	500	CUGUCGCAGCCGAUGCUG
99	561	578	AGCATCGGCTGCGACAGA	501	UCUGUCGCAGCCGAUGCU
100	562	579	GCATCGGCTGCGACAGAT	502	AUCUGUCGCAGCCGAUGC
101	563	580	CATCGGCTGCGACAGATC	503	GAUCUGUCGCAGCCGAUG
102	564	581	ATCGGCTGCGACAGATCC	504	GGAUCUGUCGCAGCCGAU
103	565	582	TCGGCTGCGACAGATCCA	505	UGGAUCUGUCGCAGCCGA
104	567	584	GGCTGCGACAGATCCAGG	506	CCUGGAUCUGUCGCAGCC
105	569	586	CTGCGACAGATCCAGGAG	507	CUCCUGGAUCUGUCGCAG
106	570	587	TGCGACAGATCCAGGAGA	508	UCUCCUGGAUCUGUCGCA
107	571	588	GCGACAGATCCAGGAGAG	509	CUCUCCUGGAUCUGUCGC

EXAMPLE 2

An ANGPTL8 siRNA conjugated to a control delivery moiety (cntrl-GalNAc) comprising 3 GalNAc groups is compared to the same siRNA conjugated to a delivery moiety of Formula I, and compared to an siRNA lacking a 5' phosphate on the antisense strand and assayed as described in this Example 2. The sense and antisense strands of the three siRNAs are shown below in Table 3; the three siRNAs each have one of the following pairs of sense and antisense strands, respectively: SEQ ID NOs: 381 and 397; or 382 and 398; or 366 and 372. Modifications are noted immediately prior to the corresponding modified nucleotide. P stands for phosphorylation, m for methylation of the OH group creating a 2' methoxy modification on the ribose; f for a 2' fluoro modification of the ribose, * for a phosphorothioate modification of the phosphodiester bond of the backbone).

Table 3.

SEQ ID NO	Sense or Anti-Sense	Sense or Anti-Sense with modifications (5' to 3')	Delivery Moiety
381	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	Control GalNAc
397	Anti-sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU	
382	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	Formula I
398	Anti-sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU	
366	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	Formula I
372	Anti-sense	mC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU	

Three assays are performed to analyze ANGPTL3/8 levels, triglyceride levels, and knockdown of ANGPTL8 expression as measured by mRNA levels (% KD), in order to compare the above siRNAs.

The conjugated siRNAs are tested in male transgenic mice for human cholesterol ester transfer protein (CETP) and apolipoprotein A1 (Taconic farms). Mice are dosed by retro-orbital injection with two adeno-associated virus (AAV) vectors. The first vector contains a plasmid with an albumin promoter and the coding sequence for human ANGPTL8 (NM_018687.7) SEQ ID NO:1. The second vector contains a mouse codon optimized sequence of human ANGPTL3 (NP_055310.1) SEQ ID NO:2. Animals are weighed and blood is collected from mice 3 to 5 weeks post AAV administration. This is considered the pre-study bleed. Serum is prepared from blood and triglycerides are measured utilizing a COBAS clinical chemistry analyzer (Roche) and ANGPTL3/8 protein levels are measured by ELISA (Meso Scale Diagnostics). Mice are assigned to groups with similar body weight, serum triglyceride and ANGPTL3/8 levels (n=6). Blood is collected on study day 0 and this collection is considered the baseline. Either PBS or test siRNAs, at doses of 3 and 10 mg/kg are administered subcutaneously to mice on study day 0. Blood is collected from mice 1 and 2 weeks post siRNA administration under isoflurane anesthesia. Serum is prepared from blood and triglycerides are measured utilizing a COBAS clinical chemistry analyzer (Roche).

Serum ANGPTL3/8 levels are measured by an ELISA(Meso Scale Diagnostics). Triglyceride as a percent change from baseline at 1 weeks is calculated as $((\text{triglyceride at one weeks} - \text{triglyceride at baseline}) / (\text{triglyceride at baseline})) * 100$. Triglyceride as a percent change from baseline at 2 weeks is calculated similarly. ANGPTL3/8 as a percent change from baseline at 1 week is calculated as $((\text{ANGPTL3/8 at one week} - \text{ANGPTL3/8 at baseline}) / (\text{ANGPTL3/8 at baseline})) * 100$. ANGPTL3/8 as a percent change from baseline at 2 weeks is calculated similarly. Serum triglyceride and ANGPTL3/8 data is analyzed for a statistically significant difference from the PBS group at corresponding timepoint using ANOVA and Dunnett's method where $p < 0.05$ was considered statistically significant (SAS Institute).

For measuring in vitro knockdown, mice are euthanized under isoflurane anesthesia two weeks post subcutaneous injection. Liver is collected from the mice and frozen in liquid nitrogen. Livers are homogenized in TriZol (Invitrogen) using Lysing Matrix D bead tubes on a FastPrep-24 (MP Bio), and RNA is purified and resuspended in nuclease free water. The RNA is quantitated on the NanoDrop (ThermoFisher). Equal amounts of RNA are reverse transcribed to cDNA using High-Capacity cDNA Reverse Transcription kit (Life Technologies) on a ProFlex Thermocycler (Thermo Fisher). Thermocycler settings are 25°C for 10 min, 37°C for 2 hrs, then 85°C for 5 min. Template cDNA is combined with Taqman Universal Master Mix and Assays on Demand primer/probesets and RT-PCR is performed on QuantStudio 7 Flex Real-Time PCR system (Applied Biosystems) with the following parameters: 50°C for 2min, 95°C for 10min then 40 cycles of 95°C for 15sec and 60°C for 1min. Fold changes (FC) are calculated as follows: the CT value of mouse Rplp0 is subtracted from CT value of human ANGPTL8 to obtain the delta CT value. The delta CT value is calculated by subtracting the average delta CT value of the untreated sample (PBS control) for each gene from the delta CT value of each test sample. Fold change is calculated by taking the log base 2 of the negative delta CT value. Percent knock down (%KD) is calculated by subtracting FC from one and multiplying by 100. Data is shown in Table 4. The two siRNAs comprising the delivery moiety of Formula I perform better than the control

delivery moiety, and demonstrate lower levels of ANGPTL8, lower triglyceride levels, and a higher percent knockdown of ANGPTL8 mRNA.

Table 4.

Sense SEQ ID NO	Anti- Sense SEQ ID NO	Dose (mg/kg)	1 week ANGPTL3/8	2 week ANGPTL3/8	1 week TRIG	2 week TRIG	% KD ANGPTL8 mRNA
381	397	3	-57*	-71*	-44*	-49*	84*
		10	-87*	-93*	-73*	-77*	97*
382	398	3	-70*	-82*	-56*	-61*	97*
		10	-93*	-96*	-74*	-77*	96*
366	372	3	-81*	-87*	-65*	-61*	96*
		10	-89*	-94*	-71*	-73*	98*

5 *indicates $p < 0.05$ ANOVA with Dunnetts

EXAMPLE 3

Exemplary siRNAs that are complementary to the above 18mer regions of the ANGPTL8 transcript NM_(SEQ ID NO:1) (Table 1), are designed and shown in the
 10 sequence listing below by the underlying nucleotide sequence, where each row represents an siRNA having the given sense and antisense strand. As shown, the underlying sense and antisense RNA oligonucleotides strands are between 18 and 23 nucleotides in length and with optional overhangs of 1 to 5 ribonucleotides. The underlying nucleotide sequence shown is modified, with 1-10 fluoro additions at the 2' position of ribose, and the remaining
 15 residues are methylated at the 2' position of ribose (creating a 2' methoxy modification). Some antisense strands are phosphorylated at the 5' position. Each siRNA is conjugated to a delivery moiety comprising 3 GalNAc groups; select delivery moieties comprise Formula I while others comprise a control moiety. One or more phosphodiester bonds are present at the 5' and 3' ends. A control GalNAc is attached at the 3' end of the sense strand. Subsets of
 20 these siRNAs are tested in an in vivo knockdown assay.

For the in vivo knockdown assay, select siRNAs are tested in male C57bl/6 mice (Taconic farms). Mice are dosed by retro-orbital injection with an adeno-associated virus

(AAV) vector containing a plasmid with an albumin promoter and the coding sequence for human ANGPTL8 (SEQ ID NO:1 (NCBI Reference Sequence NM_018687.7) (Vector BioLabs). Mice are weighed two weeks post AAV administration. Mice are assigned to groups with similar body weight (n=5). Either PBS or test siRNA, at a dose of 10 mg/kg, is administered subcutaneously to mice. Seven days post subcutaneous injection mice are euthanized under isoflurane anesthesia. Liver is collected from the mice and frozen in liquid nitrogen. RNA is isolated and purified from the collected liver and used for cDNA synthesis and quantified by RT PCR.

Fold changes (FC) are calculated as follows: the CT value of mouse Rplp0 is subtracted from CT value of human ANGPTL8 to obtain the delta CT value. Relative amount is calculated by taking the log base 2 of the negative delta delta CT value. Fold change is calculated by dividing the relative amount of each sample by the average of the control group. Percent knock down (%KD) is calculated by subtracting FC from one and multiplying by 100. Data is shown in Table 5.

Table 5

siRNA (Row Number from Table 11)	Sense SEQ ID NO	Anti-Sense SEQ ID NO	% KD
1A	124	231	64.9
3C	126	233	63.6
5E	128	235	80.6
7G	130	237	59.2
10J	133	240	71.1
40NN	151	270	72.7
43QQ	154	273	55.7
44RR	155	274	51.1
49WW	160	279	67.6
52ZZ	163	282	75.5

62D3	167	286	73.7
64F3	169	288	72.5
91P#	177	292	50.2
98V3	183	298	75.2
116f4	193	308	53.2
118h4	195	310	71.8
150H5	200	336	57.1
161S5	217	347	81.4
162TS	218	348	69.2
165W5	221	351	72.2

The same procedures described above for the 10 mg/kg dose are performed at a dose of 3 mg/kg for measuring the in vivo knockdown of the following siRNAs in Table 6. (each siRNA has the sense and antisense strands in vertical order, where the first tested siRNA comprises the first two rows of the table, SEQ ID NOs 373 and 389, the next siRNA comprises the 3rd and 4th rows of the table, SEQ ID NOs 374 and 390, and so forth; a control GalNAc is attached at the 3' end of the sense strand for each siRNA.) Abbreviations for modifications are the same as shown above in Example 3. Results for select RNAs are shown below in Table 7.

10

Table 6

SEQ ID NO	Sense or Anti-Sense	Sense or Anti-Sense with modifications (5' to 3')
373	Sense	mU*mC*mAmGmAmUmGmGfAfGfGmAmGmGmAmUmAmUmUmCmU
389	Anti-Sense	PmA*fG*mAmAmUfAmUmCmCmUmCmCmUfCmCfAmUmCmUmGmA*mG*mU
374	Sense	mG*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmU*mC*mA
390	Anti-Sense	PmU*fG*mAmAmUfAmUmCmCmUmCmCmUfCmCfAmUmCmUmGmC*mG*mU
375	Sense	mU*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmUmCmU
391	Anti-Sense	PmA*fG*mAmAmUfAmUmCmCmUmCmCmUfCmCfAmUmCmUmGmA*mG*mU
376	Sense	mU*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmU*mC*mC
392	Anti-Sense	PmG*fG*mAmAmUfAmUmCmCmUmCmCmUfCmCfAmUmCmUmGmA*mG*mU

377	Sense	mU*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmUmCmU
393	Anti-Sense	PmA*fG*mAmAmUmAmUmCmCmUmCmCmUfCmCmAmUmCmUmGmA*mG*mU
378	Sense	mC*mA*mGmAmUmGfGmAfGfGfAmGmGmAmUmAmUmUmC*mU*mA
394	Anti-Sense	PmU*fA*mGmAmAfUmAmUmCmCmUmCmCfUmCfCmAmUmCmUmG*mA*mG
379	Sense	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mA
395	Anti-Sense	PmU*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfCmUmCmCmAmU*mC*mU
380	Sense	mC*mC*mGmAmGmAfAmUfUfUfGmAmGmGmUmCmUmUmA*mA*mA
396	Anti-Sense	PmU*fU*mUmAmAfGmAmCmCmUmCmAmAfAmUfUmCmUmCmGmG*mU*mA
381	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG
397	Anti-Sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU
382	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG
398	Anti-Sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU
383	Sense	mG*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mA
399	Anti-Sense	PmU*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmC*mG*mU
384	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mA
400	Anti-Sense	PmU*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU
385	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
401	Anti-Sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU
386	Sense	mC*mG*mAmGmAmAmUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
402	Anti-Sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU
387	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
403	Anti-Sense	PmC*fU*mUmUmAmAmGmAmCmCmUmCmAfAmAmUmUmCmUmCmG*mG*mU
388	Sense	mC*mG*mAmGmAmAmUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
404	Anti-Sense	PmC*fU*mUmUmAmAmGmAmCmCmUmCmAfAmAmUmUmCmUmCmG*mG*mU

Table 7

Sense SEQ ID NO	Anti-Sense SEQ ID NO	% KD ANGPTL8 mRNA
381	397	49.8
380	396	69.2

376	392	44.3
388	404	38.9
374	390	44.7
387	403	37.9
377	393	39.1
383	399	44.9
384	400	57.8
385	401	53.8
379	395	65.1
373	389	51.8
375	391	52.7
386	402	58.9
378	394	56.8

EXAMPLE 5

GalNAc-siRNAs are tested in male transgenic mice with human cholesterol ester transfer protein (CETP) and apolipoprotein A1 (Taconic fars). The siRNAs are divided and tested in 3 studies (n=2, n=2, and n=2). Mice are dosed by retro-orbital injection with two adeno-associated virus (AAV) vectors. One vector contains a plasmid with an albumin promoter and the coding sequence for human ANGPTL8 (SEQ ID NO:1). The second vector contains a mouse codon optimized sequence of human ANGPTL3 (SEQ ID NO:2)(NP_055310.1). A Baseline blood sample is collected from mice 4 to 6.5 weeks post AAV administration. Serum is prepared from blood and triglycerides are measured utilizing a COBAS clinical chemistry analyzer (Roche) and ANGPTL3/8 is measured by ELISA (Meso Scale Diagnostics). Mice are assigned to groups with similar serum triglyceride and ANGPTL3/8 levels. siRNAs are designed as shown in Table 8; each siRNA is conjugated to a delivery moiety of Formula I. Either PBS or the siRNAs, at doses of 0.3, 1, 3 and 10mg/kg are administered subcutaneously to mice. Blood is collected from mice 3, 6, and 9 weeks post

siRNA administration under isoflurane anesthesia. Serum is prepared from blood and triglycerides are measured utilizing a COBAS clinical chemistry analyzer (Roche).

Triglyceride as a percent change from baseline at 3 weeks is calculated as $((\text{triglyceride at three weeks minus triglyceride at baseline})/(\text{triglyceride at baseline})) \times 100$.

- 5 Triglyceride as a percent change from baseline at 6 and 9 week is calculated similarly. Triglyceride Data was analyzed for a statistically significant difference from the PBS group at corresponding timepoint using ANOVA and Dunnett's method where $p < 0.05$ was considered statistically significant (SAS Institute) Data is shown in Table 9.

- 10 The corresponding in vitro percent knockdown at 1000 nM for each of the molecules is shown in Table 10.

Table 8

Sense SEQ ID NO	Sense strand sequence with modifications (5' to 3')	Anti-Sense SEQ ID NO	Antisense strand with modifications (5' to 3')
361	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mA	367	[Phos]mU*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfCmUmCmCmAmU*mC*mU
362	mC*mC*mGmAmGmAfAmUfUfUfGmAmGmGmUmCmUmUmA*mA*mA	368	[Phos]mU*fU*mUmAmAfGmAmCmUmCmAmAfAmUfUmCmUmCmGmG*mU*mA
363	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mA	369	mU*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfCmUmCmCmAmU*mC*mU
364	mG*mG*mUmCmUmUfAmAfAfGfGmCmUmCmAmCmGmCmU*mG*mA	370	mU*fC*mAmGmCfGmUmGmAmGmCmCmUfUmUfAmAmGmAmCmC*mU*mC
365	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mG	371	mC*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfCmUmCmCmAmU*mC*mU
366	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	372	mC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU

Table 9

siRNA	SEQ ID NO of Sense	SEQ ID NO of Anti-Sense	Dose (mg/kg)	3 week % chg	6 week %chg	9 week %chg	12 week %chg	15 week %chg
i	361	367	0.3	5	-4	10	-9	-13
			1	-29*	-21*	-20*	-38*	-32
			3	-62*	-56*	-45*	-50*	-50*

			10	-86*	-85*	-78*	-75*	-74*
ii	362	368	0.3	-24*	-10	-14	-33*	-19
			1	-44*	-31*	-13	-27*	-25
			3	-53*	-48*	-28*	-38*	-30
			10	-65*	-64*	-54*	-51*	-35
iii	365	371	0.3	-27	-27	-24	-41	-35
			1	-48*	-39	-38	-45	-41
			3	-81*	-72*	-72*	-73*	-64*
			10	-87*	-84*	-80*	-83*	-79*
iv	366	372	0.3	-24	-33	-27	-42	-42
			1	-57*	-51*	-46*	-56*	-48
			3	-65*	-61*	-48*	-52*	-43
			10	-76*	-73*	-60*	-61*	-55
v	363	369	0.3	-4	-8	-4	-2	-17
			1	-51*	-37*	-27*	-8	-31
			3	-73*	-66*	-55*	-60*	-50*
			10	-88*	-86*	-86*	-81*	-79*
vi	364	370	0.3	21	9	4	-5	-19
			1	-23*	-18	-16	-11	-30
			3	-42*	-34*	-23	-18	-25
			10	-72*	-63*	-54*	-42*	-50*

Table 10

siRNA	Sense SEQ ID NO	Antisense SEQ ID NO	% KD at 1000 nM
i	361	367	92.1
ii	362	368	93.7
iii	363	369	92.4
iv	364	370	77.4
v	365	371	81.0
vi	366	372	93.4

Table 11

Row	Sense Sequence	Sense SEQ ID NO	Anti-Sense Sequence	Anti-Sense SEQ ID NO
1A	GGAGCUGACCCUGCUCUCCA	124	UGGAAGAGCAGGGUCAGCUCCUC	231

2B	CCACGGAGGGACGGCUGACAA	125	UUGUCAGCCGUCCUCCGUGGUC	232
3C	ACGGCUGACAAAGGCCAGGAA	126	UUCUGGCCUUUGUCAGCCGUCC	233
4D	GGCUGACAAAGGCCAGGAACA	127	UGUUCUGGCCUUUGUCAGCCGU	234
5E	CAGGAACAGCCUGGGUCUCUA	128	UAGAGACCCAGGCUGUCCUGGC	235
6F	CAGGAACAGCCUGGGUCUCUC	129	GAGAGACCCAGGCUGUCCUGGC	236
7G	AGGAACAGCCUGGGUCUCUAU	130	AUAGAGACCCAGGCUGUCCUGG	237
8H	AGGAACAGCCUGGGUCUCUAA	131	UUAGAGACCCAGGCUGUCCUGG	238
9I	GCCUGGGUCUCUAUGGCCGCA	132	UGC GGCCAUAGAGACCCAGGCUG	239
10J	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGGC	240
11K	CUUGGUCUCUAUGGCCGCACA	134	UGUGCGGCCAUAGAGACCAAGGC	241
12L	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGUG	242
13M	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCC	243
14N	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGUU	244
15O	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAG	245
16P	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAU	246
17Q	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGGU	247
18R	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAA	248
19S	CUAGGUCUCUAUGGCCGCACA	135	UGUGCGGCCAUAGAGACCUAGGC	249
20T	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCG	250
21U	CAAGGUCUCUAUGGCCGCACA	136	UGUGCGGCCAUAGAGACCUUGGC	251
22V	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCA	252
23W	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAC	253
24X	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCU	254
25Y	CCCGGUCUCUAUGGCCGCACA	137	UGUGCGGCCAUAGAGACCGGGGC	255
26Z	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGUA	256
27AA	CAUGGUCUCUAUGGCCGCACA	138	UGUGCGGCCAUAGAGACCAUGGC	257
28BB	CAGGGUCUCUAUGGCCGCACA	139	UGUGCGGCCAUAGAGACCCUGGC	258
29CC	CGAGGUCUCUAUGGCCGCACA	140	UGUGCGGCCAUAGAGACCUCGGC	259
30DD	CGGGGUCUCUAUGGCCGCACA	141	UGUGCGGCCAUAGAGACCCGGC	260
31EE	CCAGGUCUCUAUGGCCGCACA	142	UGUGCGGCCAUAGAGACCUUGGC	261
32FF	CCGGGAUGCAGCCAGGAACU	143	AGUUCUGGGCUGCAUCCCGGCC	262
33GG	CGGGAUGCAGCCAGGAACUU	144	AAGUUCUGGGCUGCAUCCCGGC	263
34HH	AGCCCAGGAACUUCGGGCAAA	145	UUUGCCCGAAGUUCUGGGCUGC	264
35II	GCCCAGGAACUUCGGGCAAGA	146	UCUUGCCCGAAGUUCUGGGCUG	265
36JJ	CAGGAACUUCGGGCAAGCCUA	147	UAGGCUUGCCCGAAGUUCUGGG	266
37KK	AGGAACUUCGGGCAAGCCUGA	148	UCAGGCUUGCCCGAAGUUCUGG	267
38LL	AACUUCGGGCAAGCCUGUUGA	149	UCAACAGGCUUGCCCGAAGUUC	268
39MM	ACUUCGGGCAAGCCUGUUGGA	150	UCCAACAGGCUUGCCCGAAGUUC	269

40NN	UUCGGGCAAGCCUGUUGGAGA	151	UCUCCAACAGGCUUGCCCGAAGU	270
41OO	GGCAAGCCUGUUGGAGACUCA	152	UGAGUCUCCAACAGGCUUGCCCG	271
42PP	CAAGCCUGUUGGAGACUCAGA	153	UCUGAGUCUCCAACAGGCUUGCC	272
43QQ	AAGCCUGUUGGAGACUCAGAU	154	AUCUGAGUCUCCAACAGGCUUGC	273
44RR	CCUGUUGGAGACUCAGAUUGGA	155	UCCAUCUGAGUCUCCAACAGGCU	274
45SS	CUGUUGGAGACUCAGAUUGGAA	156	UCCAUCUGAGUCUCCAACAGGC	275
46TT	GGAGACUCAGAUUGGAGGAGGA	157	UCCUCCUCCAUCUGAGUCUCCAA	276
47UU	GAGACUCAGAUUGGAGGAGGAU	158	AUCCUCCUCCAUCUGAGUCUCCA	277
48VV	AGACUCAGAUUGGAGGAGGAUA	159	UAUCCUCCUCCAUCUGAGUCUCC	278
49WW	GACUCAGAUUGGAGGAGGAUAU	160	AUAUCCUCCUCCAUCUGAGUCUC	279
50XX	ACUCAGAUUGGAGGAGGAUAUU	161	AAUAUCCUCCUCCAUCUGAGUCU	280
51YY	ACUCAGAUUGGAGGAGGAUAUA	162	UAUAUCCUCCUCCAUCUGAGUCU	281
52ZZ	UCAGAUUGGAGGAGGAUAUUCU	163	AGAAUAUCCUCCUCCAUCUGAGU	282
54A3	GCAGAUUGGAGGAGGAUAUUCA	164	UGAAUAUCCUCCUCCAUCUGCGU	283
56B3	UCAGAUUGGAGGAGGAUAUUCA	165	UGAAUAUCCUCCUCCAUCUGAGU	284
57C3	UCAGAUUGGAGGAGGAUAUUC	166	GGAAUAUCCUCCUCCAUCUGAGU	285
62D3	CAGAUUGGAGGAGGAUAUUCUG	167	CAGAAUAUCCUCCUCCAUCUGAG	286
63E3	CAGAUUGGAGGAGGAUAUUCUA	168	UAGAAUAUCCUCCUCCAUCUGAG	287
64F3	AUGGAGGAGGAUAUUCUGCAG	169	CUGCAGAAUAUCCUCCUCCAUCU	288
65G3	AUGGAGGAGGAUAUUCUGCAA	170	UUGCAGAAUAUCCUCCUCCAUCU	289
69H3	AUGGAGGAGGCUAUUCUGCAG	171	CUGCAGAAUAUCCUCCUCCAUCU	288
74I3	AUGGAGGAGGUUAUUCUGCAG	172	CUGCAGAAUAUCCUCCUCCAUCU	288
80J3	AUGGAGGAGGAUAUUCUGCAG	169	CUGCAGAAUAUCCUCCUCCAUCUTTT	290
81K3	AUGGAGGAGGGUAUUCUGCAG	173	CUGCAGAAUAUCCUCCUCCAUCU	288
82L3	AUGGAGGAGGAUAUUCUGCAG	169	CUGCAGAAUAUCCUCCUCCAUCUTT	291
86M3	AGAUGGAGGAGGAUAUUCUGCAG	174	CUGCAGAAUAUCCUCCUCCAUCU	288
89N3	CAGAUUGGAGGAGGAUAUUCUGCAG	175	CUGCAGAAUAUCCUCCUCCAUCU	288
90O3	CCAGAUUGGAGGAGGAUAUUCUGCAG	176	CUGCAGAAUAUCCUCCUCCAUCU	288
91P3	GGAGGAGGAUAUUCUGCAGCU	177	AGCUGCAGAAUAUCCUCCUCCAUCU	292
92Q3	GCCAGGCACAGAAGGUGCUA	178	UAGCACCUUCUGUGCCUGGGCCA	293
93R3	AGCGGCUAGAAGUCCAGCUGA	179	UCAGCUGGACUUCUAGCCGCGUC	294
94S3	GCGGCUAGAAGUCCAGCUGAA	180	UUCAGCUGGACUUCUAGCCGCGUG	295
95T3	CGGCUAGAAGUCCAGCUGAGA	181	UCUCAGCUGGACUUCUAGCCGCGU	296
96U3	CCGAGAAUUGAGGUCUUA AAA	182	UUUAAGACCUCAAUUCUCGGUA	297
98V3	CGAGAAUUGAGGUCUUA AAG	183	CUUUAAGACCUCAAUUCUCGGU	298
99W3	GGAGAAUUGAGGUCUUA AAA	184	UUUUAAGACCUCAAUUCUCGGU	299
100X3	CGAGAAUUGAGGUCUUA AAA	185	UUUUAAGACCUCAAUUCUCGGU	300
109Y3	AGAAUUGAGGUCUUA AAGGA	186	UCCUUAAGACCUCAAUUCUCG	301

110z3	GAAUUUGAGGUCUAAAAGGCA	187	UGCCUUUAAGACCUCAAAUUCUC	302
111a4	AAUUUGAGGUCUAAAAGGCUA	188	UAGCCUUUAAGACCUCAAAUCU	303
112b4	AUUUGAGGUCUAAAAGGCUCA	189	UGAGCCUUUAAGACCUCAAAUC	304
113c4	AUCUGAGGUCUAAAAGGCUCA	190	UGAGCCUUUAAGACCUCAGAUUC	305
114d4	ACCUGAGGUCUAAAAGGCUCA	191	UGAGCCUUUAAGACCUCAGGUUC	306
115e4	UUUGAGGUCUAAAAGGCUCAA	192	UUGAGCCUUUAAGACCUCAAAUU	307
116f4	GAGGUCUUAAGGCUCACGCU	193	AGCGUGAGCCUUUAAGACCUCAA	308
117g4	GAGGUCUUAAGGCUCACGCA	194	UGCGUGAGCCUUUAAGACCUCAA	309
118h4	GGUCUUAAGGCUCACGCUGA	195	UCAGCGUGAGCCUUUAAGACCUC	310
124i4	UGUCUUAAGGCUCACGUGC	196	GCAGCGUGAGCCUUUAAGACAUC	311
126j4	GUCUUAAGGCUCACGUGAA	197	UUCAGCGUGAGCCUUUAAGACCU	312
127k4	UCUUAAGGCUCACGUGACA	198	UGUCAGCGUGAGCCUUUAAGACC	313
128l4	CCGAAAGGCUCACGUGACAA	199	UUGUCAGCGUGAGCCUUCGGAC	314
129m4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGAA	315
130n4	CACAAAGGCUCACGUGACAA	201	UUGUCAGCGUGAGCCUUUGUGAC	316
131o4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGGU	317
132p4	CCUAAAGGCUCACGUGACAA	202	UUGUCAGCGUGAGCCUUUAGGAC	318
133q4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGCA	319
134r4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGAG	320
135s4	CUGAAAGGCUCACGUGACAA	203	UUGUCAGCGUGAGCCUUCAGAC	321
136t4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGGG	322
137u4	CUCAAAGGCUCACGUGACAA	204	UUGUCAGCGUGAGCCUUUGAGAC	323
138v4	CCAAAAGGCUCACGUGACAA	205	UUGUCAGCGUGAGCCUUUUGGAC	324
139w4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGUA	325
140x4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGGC	326
141y4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGCU	327
142z4	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGGA	328
143A5	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGUG	329
144B5	CAAAAAGGCUCACGUGACAA	206	UUGUCAGCGUGAGCCUUUUUGAC	330
145C5	CGCAAAGGCUCACGUGACAA	207	UUGUCAGCGUGAGCCUUUGCGAC	331
146D5	CGAAAAGGCUCACGUGACAA	208	UUGUCAGCGUGAGCCUUUCGAC	332
147E5	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGCG	333
148F5	CAGAAAGGCUCACGUGACAA	209	UUGUCAGCGUGAGCCUUUCUGAC	334
149G5	CCCAAAGGCUCACGUGACAA	210	UUGUCAGCGUGAGCCUUUGGGAC	335
150H5	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGAC	336
151I5	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGCC	337
152J5	CUUAAAGGCUCACGUGACAA	200	UUGUCAGCGUGAGCCUUUAAGAU	338
153K5	CGUAAAGGCUCACGUGACAA	211	UUGUCAGCGUGAGCCUUUACGAC	339

154L5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGUC	340
155M5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGUU	341
156N5	CGGAAAGGCUCACGCUGACAA	212	UUGUCAGCGUGAGCCUUCCGAC	342
157O5	UUAAAGGCUCACGCUGACAAA	213	UUUGUCAGCGUGAGCCUUAAGA	343
158P5	AGGCUCACGCUGACAAGCAGA	214	UCUGCUUGUCAGCGUGAGCCUUU	344
159Q5	UGCAGCGGCAGAGGCGGGAGA	215	UCUCCCGCCUCUGCCGCUGCACG	345
160R5	GCGGCAGAGGCGGGAGAUUGU	216	ACCAUCUCCCGCCUCUGCCGCUG	346
161S5	GAGGCGGGAGAUUGGUGGCACA	217	UGUGCCACCAUCUCCCGCCUCUG	347
162T5	GCGGGAGAUUGGUGGCACAGCA	218	UGCUGUGCCACCAUCUCCCGCCU	348
163U5	GUGGCACAGCAGCAUCGGCUA	219	UAGCCGAUGCUGCUGUGCCACCA	349
164V5	CAGCAGCAUCGGCUGCGACAA	220	UUGUCGCAGCCGAUGCUGCUGG	350
165W5	AGCAGCAUCGGCUGCGACAGA	221	UCUGUCGCAGCCGAUGCUGCUGU	351
166X5	GCAGCAUCGGCUGCGACAGAA	222	UUCUGUCGCAGCCGAUGCUGCUG	352
167Y5	CAGCAUCGGCUGCGACAGAUUA	223	UAUCUGUCGCAGCCGAUGCUGCU	353
168Z5	AGCAUCGGCUGCGACAGAUCA	224	UGAUCUGUCGCAGCCGAUGCUGC	354
169a6	GCAUCGGCUGCGACAGAUCCA	225	UGGAUCUGUCGCAGCCGAUGCUG	355
170b6	CAUCGGCUGCGACAGAUCCAA	226	UUGGAUCUGUCGCAGCCGAUGCUC	356
171c6	UCGGCUGCGACAGAUCCAGGA	227	UCCUGGAUCUGUCGCAGCCGAUG	357
172d6	GGCUGCGACAGAUCCAGGAGA	228	UCUCCUGGAUCUGUCGCAGCCGA	358
173e6	GCUGCGACAGAUCCAGGAGAA	229	UUCUCCUGGAUCUGUCGCAGCCG	359
174e7	CUGCGACAGAUCCAGGAGAGA	230	UCUCUCCUGGAUCUGUCGCAGCC	360

EXAMPLE 6

- 5 To quantify levels of the Formula 1 conjugated siRNA strands in Table 13 in tissue samples, the tissue samples are homogenized in Clarity OTX cell lysis buffer (Phenomenex) to a final tissue concentration of 100 mg/ml. (For the sense strands, the OH metabolite is quantified because of rapid dephosphorylation in vivo). Plasma samples are diluted in Clarity OTX buffer 1:10 (v/v). Samples are subjected to solid phase extraction using a weak
- 10 ion exchange resin (Waters, Oasis μ Elution SPE plate). Samples are eluted and subjected to liquid chromatography-high resolution mass spectrometry (LC-HRMS) as described in ASSAY and Drug Development Technologies, 10(3) pages 278-288 (2012)

Plasma exposure in mouse or cynomolgus monkeys is measured following subcutaneous administration through 6 hrs in and 24 hrs in monkey. Liver exposure is determined in mice at 6, 24, 72, 168, 336 and 1343 hrs. Results are subjected to non-compartmental analysis using the Phoenix software NCA package. C_{max} , $t_{1/2}$ and AUC is determined in plasma for both species, liver C_{max} , $t_{1/2}$ and AUC is determined in mouse, and liver $t_{1/2}$ and AUC is determined in monkey.

Table 13 shows the liver exposure of 6 conjugated siRNAs in cynomolgus monkeys. Livers were harvested and subject to the above detection method using LC/MS about 2 and 12 weeks after treatment with subcutaneous 3 mg/kg of the listed ANGPTL8 siRNAs conjugated (at the 3' end nucleotide of the sense strand) to the GalNac containing moiety of Formula I via Linker 2 (having Formula III).

Tables 12a and 12b show two exemplary experiments of the percent knockdown of ANGPTL8 mRNA as determined by RT-PCR of liver homogenate that is harvested from cynomolgus monkeys pre (1 monkey) and post dose (several monkeys as noted below, each 3 mg/kg) of conjugated ANGPTL8 siRNAs, where the GalNac containing moiety of Formula I is conjugated to the 3' end nucleotide of the sense strand, via Linker 2 (having Formula III).

Table 12a

Cynomolgus monkey
Potency and Durability

siRNA conjugate	Sense SEQ ID NO	Antisense SEQ ID NO	15 Days ANGPTL8 mRNA (%KD $\pm$ SE from predose biopsy) 3 mg/kg	57 Days ANGPTL8 mRNA (%KD from predose biopsy) 3 mg/kg	85 Days ANGPTL8 mRNA (%KD from predose biopsy) 3 mg/kg
iii#	363	369	34	40	5
iv#	364	370	21	19	45
v*	365	371	89	79	57
vi*	366	372	69	63	12.

n=4

* n=5

Table 12b

Cynomolgus monkey
Potency and Durability

siRNA conjugate	Sense SEQ ID NO	Antisense SEQ ID NO	15 Days ANGPTL8 mRNA (%KD from predose biopsy) 3 mg/kg	57 Days ANGPTL8 mRNA (%KD from predose biopsy) 3 mg/kg	85 Days ANGPTL8 mRNA (%KD from predose biopsy) 3 mg/kg
i	361	367	88 ± 5***	74 ± 10**	63 ± 37*
ii	362	368	69 ± 31	54 ± 18	25 ± 30

5 n=6

*P ≤ 0.05, **P ≤ 0.01, *** P ≤ 0.005 vs pre-dose biopsy is statistically significant by MMRM

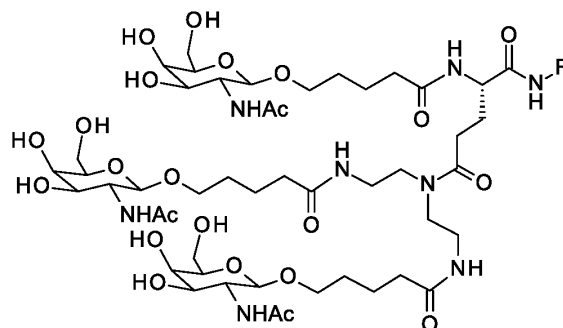
10 **Table 13**

Cynomolgus
PK Properties

siRNA conjugate	Sense SEQ ID NO	Antisense SEQ ID NO	2 week Liver exposure (µg/g)	12 week Liver exposure (µg/g)	Liver t _{1/2} (days)
i	361	367	22.0	1.9	33
ii	362	368	4.6	<0.1	<9
iii	363	369	9.0	0.1	15
iv	364	370	5.9	0.3	29
v	365	371	11.0	0.8	25
vi	366	372	5.4	0.4	30

15 The following numbered paragraphs provide additional embodiments of the RNAi agents and RNAi molecules disclosed herein:

1. An RNA interference (RNAi) molecule or RNAi agent comprising Formula I:



Formula I

and a one or more oligonucleotides comprising 15 to 40 nucleotides that bind SEQ ID NO:1 and R is conjugated to an oligonucleotide, optionally via a linker.

5

2. The RNAi molecule or RNAi agent of paragraph 1, wherein the one or more oligonucleotides that bind one or more of the sequences as set forth in Table 1 or Table 2.

10

3. The RNAi molecule or RNAi agent of paragraph 1, wherein the one or more oligonucleotides comprise a sequence as set forth in Table 2.

4. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 3, wherein the one or more oligonucleotides comprises one or more modified nucleotides.

15

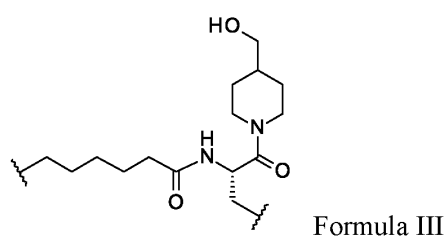
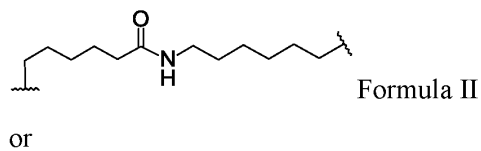
5. The RNAi molecule or RNAi agent of paragraph 4, wherein the one or more modified nucleotides are modified on the 2' position of the sugar, or on the pyrimidine or purine ring, or both.

20

6. The RNAi molecule or RNAi agent of paragraph 4 or 5, wherein the one or more modified nucleotides is a modified nucleotide comprising a modified nucleotide comprising a 2' halogenated sugar group, a modified nucleotide comprising a 2' methylated sugar group, a modified nucleotide comprising a 2' methoxylated sugar

group, a modified nucleotide comprising a methylated purine, or a modified nucleotide comprising a methylated pyrimidine ring, or any combination thereof.

- 5 7. The RNAi molecule or RNAi agent of any one of paragraphs 4 to 6, wherein the one or more modified nucleotides are modified on the 2' position of the sugar and the modification comprises one or more 2' fluoro groups or one or more 2' methoxy groups, or both.
- 10 8. The RNAi molecule or RNAi agent of any one of paragraphs 4 to 7, wherein the one or more modified nucleotides are modified on the 2' position of the sugar, and the sugar is ribose.
- 15 9. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 8, wherein the one or more oligonucleotides comprise one or more modified bonds, and wherein the one or more modified bonds is a phosphorothioate bond.
- 20 10. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 9, wherein the one or more oligonucleotides comprise an siRNA, and wherein the siRNA comprises a sense strand and an antisense strand.
- 25 11. The RNAi molecule or RNAi agent of paragraph 10, wherein the sense strand and the antisense strand are each independently between 15 to 40 nucleotides in length.
12. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 11, further comprising a linker.
13. The RNAi molecule or RNAi agent of paragraph 12, wherein the linker comprises one of the following :



- 5
14. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 13, wherein the one or more oligonucleotides comprise an siRNA.
15. The RNAi molecule or RNAi agent of paragraph 14, wherein the siRNA comprises a
- 10 sense strand and an antisense strand.
16. The RNAi molecule or RNAi agent of paragraph 15, wherein the sense strand and the antisense strand are each independently between 15 to 40 nucleotides in length.
- 15 17. The RNAi molecule or RNAi agent of any one of paragraphs 14 to 16, wherein the sense strand and the antisense strand are each independently between 18 to 25 nucleotides in length.
- 20 18. The RNAi molecule or RNAi agent of paragraph 17, wherein the sense strand and the antisense strand anneal, and optionally comprise one or more 5' or 3' nucleotide overhangs.

19. The RNAi molecule or RNAi agent of any one of paragraphs 14 to 18, wherein the 5' end of the antisense strand is optionally phosphorylated.
20. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 19, comprising a compound of Formula I and the one or more oligonucleotides that bind to any one of the sequences having SEQ ID NO:3 to SEQ ID NO:123 as shown in Table 1.
21. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 20, comprising a compound of Formula I and one or more oligonucleotides that bind to any one of the sequences shown in Table 2.
22. The RNAi molecule or RNAi agent of any of the preceding paragraphs, wherein one or more nucleotides are modified on the 2' position of the ribose.
23. The RNAi molecule or RNAi agent of any of the preceding paragraphs, wherein the ribose of at least one nucleotide is modified with a 2' fluoro group or a 2' methoxy group.
24. The RNAi molecule or RNAi agent of any of the preceding paragraphs, wherein the siRNA comprises one or more modified bonds.
25. The RNAi molecule or RNAi agent of paragraph 24, wherein the one or more modified bonds is a phosphorothioate bond.
26. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 25, wherein the siRNA comprises a sense strand comprising a sequence of any one of SEQ ID NO:361, SEQ ID NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, or SEQ ID NO:366.

27. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 25, wherein the siRNA comprises an antisense strand comprising a sequence of any one of SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, or SEQ ID NO:372.
28. The RNAi molecule or RNAi agent of any one of paragraphs 1 to 27, wherein the siRNA comprises a sense strand and an antisense strand selected from the pairs of sequences as set forth in a-f:
- a. SEQ ID NO: 361 and SEQ ID NO:367;
 - b. SEQ ID NO:362 and SEQ ID NO:368;
 - c. SEQ ID NO: 363 and SEQ ID NO:369;
 - d. SEQ ID NO: 364 and SEQ ID NO:370;
 - e. SEQ ID NO: 365 and SEQ ID NO:371; or
 - f. SEQ ID NO: 366 and SEQ ID NO:372.
29. A pharmaceutical composition comprising an RNAi molecule or RNAi agent of any one of paragraphs 1 to 28 and at least one pharmaceutically acceptable excipient.
30. A method of treating dyslipidemia comprising administering an RNAi molecule or RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.
31. A method of treating a cardiovascular disease comprising administering an effective amount of the RNAi molecule or RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.

32. A method of preventing a cardiovascular event comprising administering an effective amount of an RNAi molecule or RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.
- 5 33. The method of paragraph 32, wherein the cardiovascular event is myocardial infarction.
34. A method of decreasing hospitalizations related to cardiovascular disease or events comprising administering an RNAi molecule or RNAi agent of any one of paragraphs
10 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.
35. A method of treating non-alcoholic fatty liver disease (NAFLD) comprising administering an RNAi molecule or RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.
15
36. The method of paragraph 35, wherein the NAFLD is non-alcoholic steatohepatitis (NASH).
37. A method of lowering triglyceride levels, comprising administering an RNAi
20 molecule or RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.
38. A method of decreasing inhibition of lipoprotein lipase (LPL) comprising administering an RNAi molecule or RNAi agent of any one of paragraphs 1 to 28, or
25 a pharmaceutical composition thereof, to a patient in need thereof.
39. A method of increasing catabolism of triglyceride rich lipoproteins comprising administering an RNAi molecule or RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition thereof, to a patient in need thereof.

40. A method of treating a liver disease in a patient that would benefit from decreasing
expression levels of ANGPTL8, comprising administering an RNAi molecule or
RNAi agent of any one of paragraphs 1 to 28, or a pharmaceutical composition
5 thereof, to a patient in need thereof.

10

SEQUENCE LISTING

SEQ ID NO:1

Homo sapiens angiopoietin like 8 (ANGPTL8)

5 NCBI Reference Sequence: NM_018687.7
 ATACCTTAGA CCCTCAGTCA TGCCAGTGCC TGCTCTGTGC CTGCTCTGGG CCCTGGCAAT
 GGTGACCCGG CCTGCCTCAG CGGCCCCCAT GGGCGGCCCA GAACTGGCAC AGCATGAGGA
 GCTGACCCCTG CTCTTCCATG GGACCCTGCA GCTGGGCCAG GCCCTCAACG GTGTGTACAG
 GACCACGGAG GGACGGCTGA CAAAGGCCAG GAACAGCCTG GGTCTCTATG GCCGCACAAT
 10 AGAACTCCTG GGGCAGGAGG TCAGCCGGGG CCGGGATGCA GCCCAGGAAC TTCGGGCAAG
 CCTGTTGGAG ACTCAGATGG AGGAGGATAT TCTGCAGCTG CAGGCAGAGG CCACAGCTGA
 GGTGCTGGGG GAGGTGGCCC AGGCACAGAA GGTGCTACGG GACAGCGTGC AGCGGCTAGA
 AGTCCAGCTG AGGAGCGCCT GGCTGGGCCC TGCCTACCGA GAATTTGAGG TCTTAAAGGC
 TCACGCTGAC AAGCAGAGCC ACATCCTATG GGCCCTACA GGCCACGTGC AGCGGCAGAG
 15 GCGGGAGATG GTGCACAGC AGCATCGGCT GCGACAGATC CAGGAGAGAC TCCACACAGC
 GCGCTCCCA GCCTGAATCT GCCTGGATGG AACTGAGGAC CAATCATGCT GCAAGGAACA
 CTTCCACGCC CCGTGAGGCC CTTGTGCAGG GAGGAGCTGC CTGTTCACTG GGATCAGCCA
 GGGCGCCGGG CCCCACTTCT GAGCACAGAG CAGAGACAGA CGCAGGCGGG GACAAAGGCA
 GAGGATGTAG CCCCATTTGG GAGGGGTGGA GGAAGGACAT GTACCCTTTC ATGCCTACAC
 20 ACCCTCATT AAAGCAGAGT CGTGGCATCT CA

SEQ ID NO:2

ANGPTL3 sequence used for expression in mice

25 ATGTTACCATCAAGCTGCTGCTGTTTCATCGTGCCCTCGTGATCAGCAGCAGAATCGACCAGGACAACAGCAG
 CTTTCGACAGCCTGAGCCCCGAGCCCAAGAGCAGATTCGCCATGCTGGACGACGTGAAGATCCTGGCCAACGGCC
 TGCTGCAGCTGGGCCACGGCCTGAAGGATTTCTGTCACAAAGACCAAGGGCCAGATCAACGACATCTTCCAGAAG
 CTGAACATCTTCGACCAGAGCTTCTACGACCTGAGCCTGCAGACCAGCGAGATCAAAGAGGAAGAGAAAGAGCT
 GCGGAGGACCACCTACAAGCTGCAAGTGAAGAACGAGGAAGTGAACAAACATGAGCCTGGAAGTGAACAGCAAGC
 TGGAAGCCTGCTGGAAGAAAAGATTCTGCTGCAGCAGAAAAGTGAAGTACCTGGAAGAACAGCTGACCAACCTG
 30 ATCCAGAACCAGCCCGAGACACCCGAGCACCCTGAAGTGAACAGCCTGAAAACCTTCTGTTGAAAAGCAGGACAA
 CTCCATCAAGGACCTGCTGCAGACCGTGGAAGATCAGTACAAGCAGCTGAACCAGCAGCACTCCCAGATCAAAG
 AAATCGAGAACCAGCTGAGGCGGACCCAGCATCCAGGAACCCACCGAGATCAGCCTGTCCAGCAAGCCAGAGCC
 CCCAGAACAACCCATTCTGTCAGCTGAATGAGATCCGGAACGTGAAGCACGACGGCATCCCTGCCGAGTGCAC
 CACCATCTACAACAGAGGCGAGCACACCAGCGGGATGTACGCCATCAGACCCAGCAACAGCCAGGTGTTCCACG
 35 TGTACTGCGACGTGATCAGCGGCAGCCCTGGACACTGATCCAGCACAGAATCGATGGCAGCCAGAAGTTCAAC
 GAGACATGGGAGAACTATAAGTACGGCTTCGGCAGACTGGACGGCGAGTTTGGCTGGGCTGGAAAAGATCTA
 CAGCATCGTGAAGCAGAGCAACTACGTGCTGAGAATCGAGCTGGAAGATTGGAAGGACAACAAGCACTACATCG
 AGTACAGCTTCTACCTGGGCAACCACGAGACAACTACACCTGCACCTGGTGGCCATCACCGGCAACGTGCCA
 AACGCCATCCCCGAGAACAAGGATCTGGTGTTCAGCACCTGGGACCACAAGGCTAAGGGCCACTTCAACTGCCC
 40 CGAGGGCTACTCTGGCGGCTGGTGGTGGCATGATGAGTGCGGCGAGAACAACCTGAACGGCAAGTACAACAAGC
 CCAGGGCCAAGAGCAAGCCTGAGAGAAGAAGGGCCTGTCTGGAAGTCCCAGAACGGCAGGCTGTACTCTATC
 AAGAGCACCAAGATGCTGATCCACCCACCGACAGCGAGAGCTTCGAGTGATAA

Table 1. Target and antisense sequences for designed siRNAs

SEQ ID NO (DNA SEQ)	Start Position on DNA	End Position on DNA	18mer Target DNA Sequence (5'-3')	SEQ ID NO (RNA SEQ)	18 mer Antisense RNA sequence (5'-3')
3	120	137	AGCTGACCCTGCTCTTCC	405	GGAAGAGCAGGGUCAGCU

4	141	158	GGACCCTGCAGCTGGGCC	406	GGCCAGCUGCAGGGUCC
5	150	167	AGCTGGGCCAGGCCCTCA	407	UGAGGGCCUGGCCAGCU
6	185	202	ACGGAGGGACGGCTGACA	408	UGUCAGCCGUCCUCCGU
7	186	203	CGGAGGGACGGCTGACAA	409	UUGUCAGCCGUCCUCCG
8	191	208	GGACGGCTGACAAAGGCC	410	GGCCUUUGUCAGCCGUCC
9	194	211	CGGCTGACAAAGGCCAGG	411	CCUGGCCUUUGUCAGCCG
10	195	212	GGCTGACAAAGGCCAGGA	412	UCCUGGCCUUUGUCAGCC
11	197	214	CTGACAAAGGCCAGGAAC	413	GUUCCUGGCCUUUGUCAG
12	210	227	GGAACAGCCTGGGTCTCT	414	AGAGACCCAGGCUGUUC
13	211	228	GAACAGCCTGGGTCTCTA	415	UAGAGACCCAGGCUGUUC
14	215	232	AGCCTGGGTCTCTATGGC	416	GCCAUAGAGACCCAGGCU
15	217	234	CCTGGGTCTCTATGGCCG	417	CGGCCAUAGAGACCCAGG
16	218	235	CTGGGTCTCTATGGCCGC	418	GCGGCCAUAGAGACCCAG
17	219	236	TGGGTCTCTATGGCCGCA	419	UGCGGCCAUAGAGACCCA
18	220	237	GGGTCTCTATGGCCGCAC	420	GUGCGGCCAUAGAGACCC
19	259	276	GGTCAGCCGGGGCCGGGA	421	UCCCGGCCCGGCUGACC
20	267	284	GGGGCCGGGATGCAGCCC	422	GGGUGCAUCCCGGCCCC
21	270	287	GCCGGGATGCAGCCCAGG	423	CCUGGGCUGCAUCCCGGC
22	271	288	CCGGGATGCAGCCCAGGA	424	UCCUGGGCUGCAUCCCGG
23	273	290	GGGATGCAGCCCAGGAAC	425	GUUCCUGGGCUGCAUCCC
24	274	291	GGATGCAGCCCAGGAACT	426	AGUCCUGGGCUGCAUCC
25	281	298	GCCCAGGAACTTCGGGCA	427	UGCCCGAAGUCCUGGGC
26	282	299	CCCAGGAACTTCGGGCAA	428	UUGCCCGAAGUCCUGGG
27	283	300	CCAGGAACTTCGGGCAAG	429	CUUGCCCGAAGUCCUGG
28	284	301	CAGGAACTTCGGGCAAGC	430	GCUUGCCCGAAGUCCUG
29	285	302	AGGAACTTCGGGCAAGCC	431	GGCUUGCCCGAAGUCCU
30	286	303	GGAACCTTCGGGCAAGCCT	432	AGGCUUGCCCGAAGUCC
31	287	304	GAACTTCGGGCAAGCCTG	433	CAGGCUUGCCCGAAGUUC
32	290	307	CTTCGGGCAAGCCTGTTG	434	CAACAGGCUUGCCCGAAG
33	291	308	TTCGGGCAAGCCTGTTGG	435	CCAACAGGCUUGCCCGAA
34	293	310	CGGGCAAGCCTGTTGGAG	436	CUCCAACAGGCUUGCCCG
35	297	314	CAAGCCTGTTGGAGACTC	437	GAGUCUCCAACAGGCUUG
36	299	316	AGCCTGTTGGAGACTCAG	438	CUGAGUCUCCAACAGGCU
37	300	317	GCCTGTTGGAGACTCAGA	439	UCUGAGUCUCCAACAGGC
38	303	320	TGTTGGAGACTCAGATGG	440	CCAUCUGAGUCUCCAACA
39	304	321	GTTGGAGACTCAGATGGA	441	UCCAUCUGAGUCUCCAAC
40	309	326	AGACTCAGATGGAGGAGG	442	CCUCCUCCAUCUGAGUCU
41	310	327	GACTCAGATGGAGGAGGA	443	UCCUCCUCCAUCUGAGUC

42	311	328	ACTCAGATGGAGGAGGAT	444	AUCCUCCUCCAUCUGAGU
43	312	329	CTCAGATGGAGGAGGATA	445	UAUCCUCCUCCAUCUGAG
44	313	330	TCAGATGGAGGAGGATAT	446	AUAUCCUCCUCCAUCUGA
45	314	331	CAGATGGAGGAGGATATT	447	AAUAUCCUCCUCCAUCUG
46	315	332	AGATGGAGGAGGATATTC	448	GAAUAUCCUCCUCCAUCU
47	316	333	GATGGAGGAGGATATTCT	449	AGAAUAUCCUCCUCCAUC
48	317	334	ATGGAGGAGGATATTCTG	450	CAGAAUAUCCUCCUCCAUC
49	319	336	GGAGGAGGATATTCTGCA	451	UGCAGAAUAUCCUCCUCC
50	321	338	AGGAGGATATTCTGCAGC	452	GCUGCAGAAUAUCCUCCU
51	372	389	AGGTGGCCAGGCACAGA	453	UCUGUGCCUGGCCACCU
52	379	396	CCAGGCACAGAAGGTGCT	454	AGCACCUUCUGUGCCUGG
53	411	428	AGCGGCTAGAAGTCCAGC	455	GCUGGACUUCUAGCCGCU
54	412	429	GCGGCTAGAAGTCCAGCT	456	AGCUGGACUUCUAGCCGC
55	413	430	CGGCTAGAAGTCCAGCTG	457	CAGCUGGACUUCUAGCCG
56	414	431	GGCTAGAAGTCCAGCTGA	458	UCAGCUGGACUUCUAGCC
57	415	432	GCTAGAAGTCCAGCTGAG	459	CUCAGCUGGACUUCUAGC
58	420	437	AAGTCCAGCTGAGGAGCG	460	CGCUCCUCAGCUGGACUU
59	421	438	AGTCCAGCTGAGGAGCGC	461	GCGCUCCUCAGCUGGACU
60	438	455	CCTGGCTGGGCCCTGCCT	462	AGGCAGGGCCCAGCCAGG
61	459	476	GAGAATTTGAGGTCTTAA	463	UUAAGACCUCAAAUCUC
62	460	477	AGAATTTGAGGTCTTAAA	464	UUUAAGACCUCAAAUCU
63	462	479	AATTTGAGGTCTTAAAGG	465	CCUUUAAGACCUCAAAUC
64	463	480	ATTTGAGGTCTTAAAGGC	466	GCCUUUAAGACCUCAAAUC
65	464	481	TTTGAGGTCTTAAAGGCT	467	AGCCUUUAAGACCUCAAA
66	465	482	TTGAGGTCTTAAAGGCTC	468	GAGCCUUUAAGACCUCAA
67	466	483	TGAGGTCTTAAAGGCTCA	469	UGAGCCUUUAAGACCUC
68	467	484	GAGGTCTTAAAGGCTCAC	470	GUGAGCCUUUAAGACCUC
69	469	486	GGTCTTAAAGGCTCACGC	471	GCGUGAGCCUUUAAGACC
70	471	488	TCTTAAAGGCTCACGCTG	472	CAGCGUGAGCCUUUAAGA
71	472	489	CTTAAAGGCTCACGCTGA	473	UCAGCGUGAGCCUUUAAG
72	473	490	TTAAAGGCTCACGCTGAC	474	GUCAGCGUGAGCCUUUA
73	474	491	TAAAGGCTCACGCTGACA	475	UGUCAGCGUGAGCCUUUA
74	475	492	AAAGGCTCACGCTGACAA	476	UUGUCAGCGUGAGCCUUU
75	476	493	AAGGCTCACGCTGACAAG	477	CUUGUCAGCGUGAGCCUU
76	477	494	AGGCTCACGCTGACAAGC	478	GCUUGUCAGCGUGAGCCU
77	479	496	GCTCACGCTGACAAGCAG	479	CUGCUUGUCAGCGUGAGC
78	480	497	CTCACGCTGACAAGCAGA	480	UCUGCUUGUCAGCGUGAG
79	481	498	TCACGCTGACAAGCAGAG	481	CUCUGCUUGUCAGCGUGA

80	482	499	CACGCTGACAAGCAGAGC	482	GCUCUGCUUGUCAGCGUG
81	483	500	ACGCTGACAAGCAGAGCC	483	GGCUCUGCUUGUCAGCGU
82	485	502	GCTGACAAGCAGAGCCAC	484	GUGGCUUGUCUUGUCAGC
83	513	530	CCCTCACAGGCCACGTGC	485	GCACGUGGCCUGUGAGGG
84	514	531	CCTCACAGGCCACGTGCA	486	UGCACGUGGCCUGUGAGG
85	520	537	AGGCCACGTGCAGCGGCA	487	UGCCGUGCAGCUGGGCCU
86	521	538	GGCCACGTGCAGCGGCAG	488	CUGCCGUGCAGCUGGGCC
87	524	541	CACGTGCAGCGGCAGAGG	489	CCUCUGCCGUGCAGCUG
88	530	547	CAGCGGCAGAGGCGGGAG	490	CUCCCGCCUCUGCCGUG
89	534	551	GGCAGAGGCGGGAGATGG	491	CCAUCUCCCGCCUCUGCC
90	540	557	GGCGGGAGATGGTGGCAC	492	GUGCCACCAUCUCCCGCC
91	543	560	GGGAGATGGTGGCACAGC	493	GCUGUGCCACCAUCUCC
92	546	563	AGATGGTGGCACAGCAGC	494	GCUGCUGUGCCACCAUCU
93	553	570	GGCACAGCAGCATCGGCT	495	AGCCGAUGCUGCUGUGCC
94	555	572	CACAGCAGCATCGGCTGC	496	GCAGCCGAUGCUGCUGUG
95	557	574	CAGCAGCATCGGCTGCGA	497	UCGCAGCCGAUGCUGCUG
96	558	575	AGCAGCATCGGCTGCGAC	498	GUCGCAGCCGAUGCUGCU
97	559	576	GCAGCATCGGCTGCGACA	499	UGUCGCAGCCGAUGCUGC
98	560	577	CAGCATCGGCTGCGACAG	500	CUGUCGCAGCCGAUGCUG
99	561	578	AGCATCGGCTGCGACAGA	501	UCUGUCGCAGCCGAUGC
100	562	579	GCATCGGCTGCGACAGAT	502	AUCUGUCGCAGCCGAUGC
101	563	580	CATCGGCTGCGACAGATC	503	GAUCUGUCGCAGCCGAUG
102	564	581	ATCGGCTGCGACAGATCC	504	GGAUCUGUCGCAGCCGAU
103	565	582	TCGGCTGCGACAGATCCA	505	UGGAUCUGUCGCAGCCGA
104	567	584	GGCTGCGACAGATCCAGG	506	CCUGGAUCUGUCGCAGCC
105	569	586	CTGCGACAGATCCAGGAG	507	CUCCUGGAUCUGUCGCAG
106	570	587	TGCGACAGATCCAGGAGA	508	UCUCCUGGAUCUGUCGCA
107	571	588	GCGACAGATCCAGGAGAG	509	CUCUCCUGGAUCUGUCGC
108	607	624	CCCAGCCTGAATCTGCCT	510	AGGCAGAUUCAGGCUGGG
109	610	627	AGCCTGAATCTGCCTGGA	511	UCCAGGCAGAUUCAGGCU
110	611	628	GCCTGAATCTGCCTGGAT	512	AUCCAGGCAGAUUCAGGC
111	619	636	CTGCCTGGATGGAAGTGA	513	UCAGUCCAUCAGGCAG
112	644	661	TCATGCTGCAAGGAACAC	514	GUGUCCUUGCAGCAUGA
113	652	669	CAAGGAACACTTCCACGC	515	GCGUGGAAGUGUCCUUG
114	655	672	GGAACACTTCCACGCCCC	516	GGGGCGUGGAAGUGUCC
115	698	715	TGCCTGTTCACCTGGGATC	517	GAUCCAGUGAAGCAGGCA
116	699	716	GCCTGTTCACCTGGGATCA	518	UGAUCCAGUGAAGCAGGC
117	701	718	CTGTTCACCTGGGATCAGC	519	GCUGAUCCAGUGAAGACG

118	702	719	TGTTCACTGGGATCAGCC	520	GGCUGAUCCCAGUGAACA
119	709	726	TGGGATCAGCCAGGGCGC	521	GCGCCUGGCUGAUCCCA
120	710	727	GGGATCAGCCAGGGCGCC	522	GGCGCCUGGCUGAUCCC
121	847	864	CATTAAAGCAGAGTCGTG	523	CACGACUCUGCUUUAUG
122	848	865	ATTAAAGCAGAGTCGTGG	524	CCACGACUCUGCUUUAU
123	850	867	TAAAGCAGAGTCGTGGCA	525	UGCCACGACUCUGCUUUA

Table 2.

SEQ ID NO (DNA SEQ)	Start Position on DNA	End Position on DNA	18mer DNA Sequence (5'-3')	SEQ ID NO (RNA SEQ)	Antisense RNA sequence (5' - 3')
3	120	137	AGCTGACCCTGCTCTTCC	405	GGAAGAGCAGGGUCAGCU
6	185	202	ACGGAGGGACGGCTGACA	408	UGUCAGCCGUCCUCCGU
10	195	212	GGCTGACAAAGGCCAGGA	412	UCCUGGCCUUUGUCAGCC
11	197	214	CTGACAAAGGCCAGGAAC	413	GUUCCUGGCCUUUGUCAG
12	210	227	GGAACAGCCTGGGTCTCT	414	AGAGACCCAGGCUGUUC
13	211	228	GAACAGCCTGGGTCTCTA	415	UAGAGACCCAGGCUGUUC
16	218	235	CTGGGTCTCTATGGCCGC	418	GCGGCCAUAGAGACCCAG
18	220	237	GGGTCTCTATGGCCGCAC	420	GUGCGGCCAUAGAGACCC
23	273	290	GGGATGCAGCCCAGGAAC	425	GUUCCUGGGCUGCAUCCC
24	274	291	GGATGCAGCCCAGGAACT	426	AGUUCUGGGCUGCAUCC
26	282	299	CCCAGGAACTTCGGGCAA	428	UUGCCCGAAGUUCUGGG
27	283	300	CCAGGAACTTCGGGCAAG	429	CUUGCCCGAAGUUCUGG
30	286	303	GGAACCTTCGGGCAAGCCT	432	AGGCUUGCCCGAAGUUC
31	287	304	GAACCTTCGGGCAAGCCTG	433	CAGGCUUGCCCGAAGUUC
32	290	307	CTTCGGGCAAGCCTGTTG	434	CAACAGGCUUGCCCGAAG
33	291	308	TTCGGGCAAGCCTGTTGG	435	CCAACAGGCUUGCCCGAA
34	293	310	CGGGCAAGCCTGTTGGAG	436	CUCCAACAGGCUUGCCCG
35	297	314	CAAGCCTGTTGGAGACTC	437	GAGUCUCCAACAGGCUUG
36	299	316	AGCCTGTTGGAGACTCAG	438	CUGAGUCUCCAACAGGCU
37	300	317	GCCTGTTGGAGACTCAGA	439	UCUGAGUCUCCAACAGGC
38	303	320	TGTTGGAGACTCAGATGG	440	CCAUCUGAGUCUCCAACA
39	304	321	GTTGGAGACTCAGATGGA	441	UCCAUCUGAGUCUCCAAC
40	309	326	AGACTCAGATGGAGGAGG	442	CCUCCUCCAUCUGAGUCU
41	310	327	GACTCAGATGGAGGAGGA	443	UCCUCCUCCAUCUGAGUC
42	311	328	ACTCAGATGGAGGAGGAT	444	AUCCUCCUCCAUCUGAGU
43	312	329	CTCAGATGGAGGAGGATA	445	UAUCCUCCUCCAUCUGAG

44	313	330	TCAGATGGAGGAGGATAT	446	AUAUCCUCCUCCAUCUGA
46	315	332	AGATGGAGGAGGATATTC	448	GAAUAUCCUCCUCCAUCU
47	316	333	GATGGAGGAGGATATTCT	449	AGAAUAUCCUCCUCCAUC
49	319	336	GGAGGAGGATATTCTGCA	451	UGCAGAAUAUCCUCCUCC
50	321	338	AGGAGGATATTCTGCAGC	452	GCUGCAGAAUAUCCUCCU
52	379	396	CCAGGCACAGAAGGTGCT	454	AGCACCUUCUGUGCCUGG
55	413	430	CGGCTAGAAGTCCAGCTG	457	CAGCUGGACUUCUAGCCG
56	414	431	GGCTAGAAGTCCAGCTGA	458	UCAGCUGGACUUCUAGCC
57	415	432	GCTAGAAGTCCAGCTGAG	459	CUCAGCUGGACUUCUAGC
61	459	476	GAGAATTTGAGGTCTTAA	463	UUAAGACCUCAAAUCUC
62	460	477	AGAATTTGAGGTCTTAAA	464	UUUAAGACCUCAAAUCU
63	462	479	AATTTGAGGTCTTAAAGG	465	CCUUUAAGACCUCAAAUU
64	463	480	ATTTGAGGTCTTAAAGGC	466	GCCUUUAAGACCUCAAAU
65	464	481	TTTGAGGTCTTAAAGGCT	467	AGCCUUUAAGACCUCAAA
66	465	482	TTGAGGTCTTAAAGGCTC	468	GAGCCUUUAAGACCUCAA
67	466	483	TGAGGTCTTAAAGGCTCA	469	UGAGCCUUUAAGACCUCA
69	469	486	GGTCTTAAAGGCTCACGC	471	GCGUGAGCCUUUAAGACC
70	471	488	TCTTAAAGGCTCACGCTG	472	CAGCGUGAGCCUUUAAGA
71	472	489	CTTAAAGGCTCACGCTGA	473	UCAGCGUGAGCCUUUAAG
72	473	490	TTAAAGGCTCACGCTGAC	474	GUCAGCGUGAGCCUUUAA
73	474	491	TAAAGGCTCACGCTGACA	475	UGUCAGCGUGAGCCUUUA
74	475	492	AAAGGCTCACGCTGACAA	476	UUGUCAGCGUGAGCCUUU
77	479	496	GCTCACGCTGACAAGCAG	479	CUGCUUGUCAGCGUGAGC
88	530	547	CAGCGGCAGAGGCGGGAG	490	CUCCCGCCUCUGCCGCUG
89	534	551	GGCAGAGGCGGGAGATGG	491	CCAUCUCCCGCCUCUGCC
90	540	557	GGCGGGAGATGGTGGCAC	492	GUGCCACCAUCUCCCGCC
91	543	560	GGGAGATGGTGGCACAGC	493	GCUGUGCCACCAUCUCCC
93	553	570	GGCACAGCAGCATCGGCT	495	AGCCGAUGCUGCUGUGCC
97	559	576	GCAGCATCGGCTGCGACA	499	UGUCGCAGCCGAUGCUGC
98	560	577	CAGCATCGGCTGCGACAG	500	CUGUCGCAGCCGAUGCUG
99	561	578	AGCATCGGCTGCGACAGA	501	UCUGUCGCAGCCGAUGCU
100	562	579	GCATCGGCTGCGACAGAT	502	AUCUGUCGCAGCCGAUGC
101	563	580	CATCGGCTGCGACAGATC	503	GAUCUGUCGCAGCCGAUG
102	564	581	ATCGGCTGCGACAGATCC	504	GGAUCUGUCGCAGCCGAU
103	565	582	TCGGCTGCGACAGATCCA	505	UGGAUCUGUCGCAGCCGA
104	567	584	GGCTGCGACAGATCCAGG	506	CCUGGAUCUGUCGCAGCC
105	569	586	CTGCGACAGATCCAGGAG	507	CUCCUGGAUCUGUCGCAG
106	570	587	TGCGACAGATCCAGGAGA	508	UCUCCUGGAUCUGUCGCA

107	571	588	GCGACAGATCCAGGAGAG	509	CUCUCCUGGAUCUGUCGC
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Table 3.

SEQ ID NO	Sense or Anti-Sense	Sense or Anti-Sense with modifications (5' to 3')	Delivery Moiety
381	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	Control GalNAc
397	Anti-sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU	
382	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	Formula I
398	Anti-sense	PmC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU	
366	Sense	mC*mG*mAmGmAmAfUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG	Formula I
372	Anti-sense	mC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfUmUmCmUmCmG*mG*mU	

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Table 6

SEQ ID NO	Sense or Anti-Sense	Sense or Anti-Sense with modifications (5' to 3')
373	Sense	mU*mC*mAmGmAmUmGmGfAfGfGmAmGmGmAmUmAmUmUmCmU
389	Anti-Sense	PmA*fG*mAmAmUfAmUmCmCmUmCmUmUfCmCfAmUmCmUmGmA*mG*mU
374	Sense	mG*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmU*mC*mA
390	Anti-Sense	PmU*fG*mAmAmUfAmUmCmCmUmCmUmUfCmCfAmUmCmUmGmC*mG*mU
375	Sense	mU*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmUmCmU
391	Anti-Sense	PmA*fG*mAmAmUfAmUmCmCmUmCmUmUfCmCfAmUmCmUmGmA*mG*mU
376	Sense	mU*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmU*mC*mC
392	Anti-Sense	PmG*fG*mAmAmUfAmUmCmCmUmCmUmUfCmCfAmUmCmUmGmA*mG*mU
377	Sense	mU*mC*mAmGmAmUfGmGfAfGfGmAmGmGmAmUmAmUmUmCmU
393	Anti-Sense	PmA*fG*mAmAmUmAmUmCmCmUmCmUmUfCmCmAmUmCmUmGmA*mG*mU
378	Sense	mC*mA*mGmAmUmGfGmAfGfGfAmGmGmAmUmAmUmUmC*mU*mA
394	Anti-Sense	PmU*fA*mGmAmAfUmAmUmCmCmUmCmUfUmCfCmAmUmCmUmG*mA*mG
379	Sense	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mA

395	Anti-Sense	PmU*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfCmUmCmCmA*U*mC*mU
380	Sense	mC*mC*mGmAmGmAfAmUfUfUfGmAmGmGmUmCmUmAmA*mA*mA
396	Anti-Sense	PmU*fU*mUmAmA fGmAmCmCmUmCmA fAmUfUmCmUmCmGmG*mU*mA
381	Sense	mC*mG*mAmGmAmA fUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG
397	Anti-Sense	PmC*fU*mUmUmA fAmGmAmCmCmUmCmA fAmA fUmUmCmUmCmG*mG*mU
382	Sense	mC*mG*mAmGmAmA fUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mG
398	Anti-Sense	PmC*fU*mUmUmA fAmGmAmCmCmUmCmA fAmA fUmUmCmUmCmG*mG*mU
383	Sense	mG*mG*mAmGmAmA fUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mA
399	Anti-Sense	PmU*fU*mUmUmA fAmGmAmCmCmUmCmA fAmA fUmUmCmUmCmC*mG*mU
384	Sense	mC*mG*mAmGmAmA fUmUfUfGfAmGmGmUmCmUmUmAmA*mA*mA
400	Anti-Sense	PmU*fU*mUmUmA fAmGmAmCmCmUmCmA fAmA fUmUmCmUmCmG*mG*mU
385	Sense	mC*mG*mAmGmAmA fUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
401	Anti-Sense	PmC*fU*mUmUmA fAmGmAmCmCmUmCmA fAmA fUmUmCmUmCmG*mG*mU
386	Sense	mC*mG*mAmGmAmAmUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
402	Anti-Sense	PmC*fU*mUmUmA fAmGmAmCmCmUmCmA fAmA fUmUmCmUmCmG*mG*mU
387	Sense	mC*mG*mAmGmAmA fUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
403	Anti-Sense	PmC*fU*mUmUmAmAmGmAmCmCmUmCmA fAmAmUmUmCmUmCmG*mG*mU
388	Sense	mC*mG*mAmGmAmAmUmUfUfGfAmGmGmUmCmUmUmAmAmAmG
404	Anti-Sense	PmC*fU*mUmUmAmAmGmAmCmCmUmCmA fAmAmUmUmCmUmCmG*mG*mU

Table 8

Sense SEQ ID NO	Sense strand sequence with modifications (5' to 3')	Anti-Sense SEQ ID NO	Antisense strand with modifications (5' to 3')
361	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mA	367	[Phos]mU*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfCmUmCmCmA*U*mC*mU
362	mC*mC*mGmAmGmAfAmUfUfUfGmAmGmGmUmCmUmUmAmA*mA*mA	368	[Phos]mU*fU*mUmAmA fGmAmCmCmUmCmA fAmUfUmCmUmCmGmG*mU*mA
363	mA*mU*mGmGmAmGfGmAfGfGfAmUmAmUmUmCmUmGmC*mA*mA	369	mU*fU*mGmCmA fGmAmAmUmAmUmCmCfUmCfCmUmCmCmA*U*mC*mU

364	mG*mG*mUmCmUmUfAmAfAfGfGmCmU mCmAmCmGmCmU*mG*mA	370	mU*fC*mAmGmCfGmUmGmAmGmCmUfUmUfA mAmGmAmCmC*mU*mC
365	mA*mU*mGmGmAmGfGmAfGfGfAmUmA mUmUmCmUmGmC*mA*mG	371	mC*fU*mGmCmAfGmAmAmUmAmUmCmCfUmCfC mUmCmCmAmU*mC*mU
366	mC*mG*mAmGmAmAfUmUfUfGfAmGmG mUmCmUmUmAmA*mA*mG	372	mC*fU*mUmUmAfAmGmAmCmCmUmCmAfAmAfU mUmCmUmCmG*mG*mU

Table 11

Row	Sense Sequence	Sense SEQ ID NO	Anti-Sense Sequence	Anti- Sense SEQ ID NO
1A	GGAGCUGACCCUGCUCUCCA	124	UGGAAGAGCAGGGUCAGCUCCUC	231
2B	CCACGGAGGGACGGCUGACAA	125	UUGUCAGCCGUCCCUCGUGGUC	232
3C	ACGGCUGACAAAGGCCAGGAA	126	UUCUGGGCCUUUGUCAGCCGUCC	233
4D	GGCUGACAAAGGCCAGGAACA	127	UGUUCUGGGCCUUUGUCAGCCGU	234
5E	CAGGAACAGCCUGGGUCUCUA	128	UAGAGACCCAGGCUGUCCUGGC	235
6F	CAGGAACAGCCUGGGUCUCUC	129	GAGAGACCCAGGCUGUCCUGGC	236
7G	AGGAACAGCCUGGGUCUCUAU	130	AUAGAGACCCAGGCUGUCCUGG	237
8H	AGGAACAGCCUGGGUCUCUAA	131	UUAGAGACCCAGGCUGUCCUGG	238
9I	GCCUGGGUCUCUAUGGCCGCA	132	UGC GGCCA UAGAGACCCAGGCUG	239
10J	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGGC	240
11K	CUUGGUCUCUAUGGCCGCACA	134	UGUGCGGCCAUAGAGACCAAGGC	241
12L	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGUG	242
13M	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCC	243
14N	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGUU	244
15O	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAG	245
16P	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAU	246
17Q	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGGU	247
18R	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAA	248
19S	CUAGGUCUCUAUGGCCGCACA	135	UGUGCGGCCAUAGAGACCUAGGC	249
20T	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCG	250
21U	CAAGGUCUCUAUGGCCGCACA	136	UGUGCGGCCAUAGAGACCUUGGC	251
22V	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCA	252
23W	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGAC	253
24X	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGCU	254
25Y	CCCGGUCUCUAUGGCCGCACA	137	UGUGCGGCCAUAGAGACCGGGGC	255
26Z	CUGGGUCUCUAUGGCCGCACA	133	UGUGCGGCCAUAGAGACCCAGUA	256
27AA	CAUGGUCUCUAUGGCCGCACA	138	UGUGCGGCCAUAGAGACCAUGGC	257
28BB	CAGGGUCUCUAUGGCCGCACA	139	UGUGCGGCCAUAGAGACCCUGGC	258

29CC	CGAGGUCUCUAUGGCCGCACA	140	UGUGCGGCCAUAGAGACCUCGGC	259
30DD	CGGGGUCUCUAUGGCCGCACA	141	UGUGCGGCCAUAGAGACCCCGGC	260
31EE	CCAGGUCUCUAUGGCCGCACA	142	UGUGCGGCCAUAGAGACCUGGGC	261
32FF	CCGGGAUGCAGCCAGGAACU	143	AGUUCCUGGGCUGCAUCCCGGC	262
33GG	CGGGAUGCAGCCAGGAACUU	144	AAGUCCUGGGCUGCAUCCCGGC	263
34HH	AGCCCAGGAACUUCGGGCAA	145	UUUGCCCAGAGUUCUGGGCUGC	264
35II	GCCCAGGAACUUCGGGCAAGA	146	UCUUGCCCAGAGUUCUGGGCUG	265
36JJ	CAGGAACUUCGGGCAAGCCUA	147	UAGGCUUGCCCAGAGUUCUGGG	266
37KK	AGGAACUUCGGGCAAGCCUGA	148	UCAGGCUUGCCCAGAGUUCUGG	267
38LL	AACUUCGGGCAAGCCUGUUGA	149	UCAACAGGCUUGCCCAGAGUUC	268
39MM	ACUUCGGGCAAGCCUGUUGGA	150	UCCAACAGGCUUGCCCAGAGUUC	269
40NN	UUCGGGCAAGCCUGUUGGAGA	151	UCUCCAACAGGCUUGCCCAGAGU	270
41OO	GGCAAGCCUGUUGGAGACUCA	152	UGAGUCUCCAACAGGCUUGCCCG	271
42PP	CAAGCCUGUUGGAGACUCAGA	153	UCUGAGUCUCCAACAGGCUUGCC	272
43QQ	AAGCCUGUUGGAGACUCAGAU	154	AUCUGAGUCUCCAACAGGCUUGC	273
44RR	CCUGUUGGAGACUCAGAUUGGA	155	UCCAUCUGAGUCUCCAACAGGCU	274
45SS	CUGUUGGAGACUCAGAUUGGAA	156	UCCAUCUGAGUCUCCAACAGGC	275
46TT	GGAGACUCAGAUUGGAGGAGGA	157	UCCUCCUCCAUCUGAGUCUCCAA	276
47UU	GAGACUCAGAUUGGAGGAGGAU	158	AUCCUCCUCCAUCUGAGUCUCCA	277
48VV	AGACUCAGAUUGGAGGAGGAUA	159	UAUCCUCCUCCAUCUGAGUCUCC	278
49WW	GACUCAGAUUGGAGGAGGAUAU	160	AUAUCCUCCUCCAUCUGAGUCUC	279
50XX	ACUCAGAUUGGAGGAGGAUAUU	161	AAUAUCCUCCUCCAUCUGAGUCU	280
51YY	ACUCAGAUUGGAGGAGGAUAUA	162	UAUAUCCUCCUCCAUCUGAGUCU	281
52ZZ	UCAGAUUGGAGGAGGAUAUUCU	163	AGAAUAUCCUCCUCCAUCUGAGU	282
54A3	GCAGAUUGGAGGAGGAUAUUCA	164	UGAAUAUCCUCCUCCAUCUGCGU	283
56B3	UCAGAUUGGAGGAGGAUAUUCA	165	UGAAUAUCCUCCUCCAUCUGAGU	284
57C3	UCAGAUUGGAGGAGGAUAUUC	166	GGAAUAUCCUCCUCCAUCUGAGU	285
62D3	CAGAUUGGAGGAGGAUAUUCUG	167	CAGAAUAUCCUCCUCCAUCUGAG	286
63E3	CAGAUUGGAGGAGGAUAUUCUA	168	UAGAAUAUCCUCCUCCAUCUGAG	287
64F3	AUGGAGGAGGAUAUUCUGCAG	169	CUGCAGAAUAUCCUCCUCCAUCU	288
65G3	AUGGAGGAGGAUAUUCUGCAA	170	UUGCAGAAUAUCCUCCUCCAUCU	289
69H3	AUGGAGGAGGCUAUUCUGCAG	171	CUGCAGAAUAUCCUCCUCCAUCU	288
74I3	AUGGAGGAGGUUAUUCUGCAG	172	CUGCAGAAUAUCCUCCUCCAUCU	288
80J3	AUGGAGGAGGAUAUUCUGCAG	169	CUGCAGAAUAUCCUCCUCCAUCUTTT	290
81K3	AUGGAGGAGGGUAUUCUGCAG	173	CUGCAGAAUAUCCUCCUCCAUCU	288
82L3	AUGGAGGAGGAUAUUCUGCAG	169	CUGCAGAAUAUCCUCCUCCAUCUTT	291
86M3	AGAUGGAGGAGGAUAUUCUGCAG	174	CUGCAGAAUAUCCUCCUCCAUCU	288
89N3	CAGAUUGGAGGAGGAUAUUCUGCAG	175	CUGCAGAAUAUCCUCCUCCAUCU	288

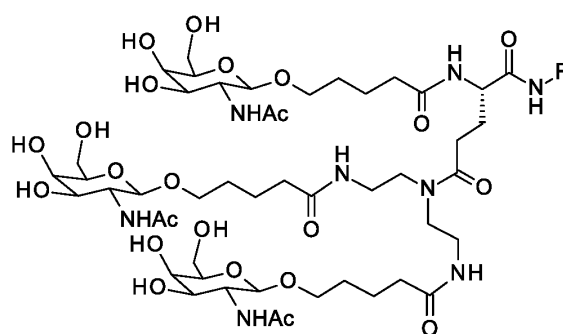
9003	CCAGAUGGAGGAGGAUAUUCUGCAG	176	CUGCAGAAUAUCCUCCUCCAUCU	288
91P3	GGAGGAGGAUAUUCUGCAGCU	177	AGCUGCAGAAUAUCCUCCUCCA	292
92Q3	GCCCAGGCACAGAAGGUGCUA	178	UAGCACCUUCUGUGCCUGGGCCA	293
93R3	AGCGGCUAGAAGUCCAGCUGA	179	UCAGCUGGACUUCUAGCCGCGC	294
94S3	GCGGCUAGAAGUCCAGCUGAA	180	UUCAGCUGGACUUCUAGCCGCGC	295
95T3	CGGCUAGAAGUCCAGCUGAGA	181	UCUCAGCUGGACUUCUAGCCGCGC	296
96U3	CCGAGAAUUGAGGUCUUA	182	UUUAAGACCUCAAAUCUCGGUA	297
98V3	CGAGAAUUGAGGUCUUAAG	183	CUUUAAGACCUCAAAUCUCGGU	298
99W3	GGAGAAUUGAGGUCUUA	184	UUUAAGACCUCAAAUCUCGGU	299
100X3	CGAGAAUUGAGGUCUUA	185	UUUAAGACCUCAAAUCUCGGU	300
109Y3	AGAAUUGAGGUCUUAAGGA	186	UCCUUAAGACCUCAAAUCUCG	301
110Z3	GAAUUGAGGUCUUAAGGCA	187	UGCCUUAAGACCUCAAAUCUC	302
111a4	AAUUGAGGUCUUAAGGCUA	188	UAGCCUUAAGACCUCAAAUCU	303
112b4	AUUGAGGUCUUAAGGCUCA	189	UGAGCCUUAAGACCUCAAAUC	304
113c4	AUCUGAGGUCUUAAGGCUCA	190	UGAGCCUUAAGACCUCAGAUUC	305
114d4	ACCUGAGGUCUUAAGGCUCA	191	UGAGCCUUAAGACCUCAGGUUC	306
115e4	UUUGAGGUCUUAAGGCUCAA	192	UUGAGCCUUAAGACCUCAAAUC	307
116f4	GAGGUCUUAAGGCUACGCU	193	AGCGUGAGCCUUAAGACCUCAA	308
117g4	GAGGUCUUAAGGCUACGCA	194	UGCGUGAGCCUUAAGACCUCAA	309
118h4	GGUCUUAAGGCUACGCUGA	195	UCAGCGUGAGCCUUAAGACCUC	310
124i4	UGUCUUAAGGCUACGCUGC	196	GCAGCGUGAGCCUUAAGACAUC	311
126j4	GUCUUAAGGCUACGCUGAA	197	UUCAGCGUGAGCCUUAAGACCUC	312
127k4	UCUUAAGGCUACGCUGACA	198	UGUCAGCGUGAGCCUUAAGACC	313
128l4	CCGAAAGGCUACGCUGACAA	199	UUGUCAGCGUGAGCCUUCGGAC	314
129m4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGAA	315
130n4	CACAAAGGCUACGCUGACAA	201	UUGUCAGCGUGAGCCUUGUGAC	316
131o4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGGU	317
132p4	CCUAAAGGCUACGCUGACAA	202	UUGUCAGCGUGAGCCUUAAGGAC	318
133q4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGCA	319
134r4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGAG	320
135s4	CUGAAAGGCUACGCUGACAA	203	UUGUCAGCGUGAGCCUUCAGAC	321
136t4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGGG	322
137u4	CUCAAAGGCUACGCUGACAA	204	UUGUCAGCGUGAGCCUUGAGAC	323
138v4	CCAAAAGGCUACGCUGACAA	205	UUGUCAGCGUGAGCCUUGGAC	324
139w4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGUA	325
140x4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGGC	326
141y4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGCU	327
142z4	CUUAAAGGCUACGCUGACAA	200	UUGUCAGCGUGAGCCUUAAGGA	328

143A5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGUG	329
144B5	CAAAAAGGCUCACGCUGACAA	206	UUGUCAGCGUGAGCCUUUUUGAC	330
145C5	CGAAAAGGCUCACGCUGACAA	207	UUGUCAGCGUGAGCCUUUGCGAC	331
146D5	CGAAAAGGCUCACGCUGACAA	208	UUGUCAGCGUGAGCCUUUUCGAC	332
147E5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGCG	333
148F5	CAGAAAAGGCUCACGCUGACAA	209	UUGUCAGCGUGAGCCUUUCUGAC	334
149G5	CCCAAAGGCUCACGCUGACAA	210	UUGUCAGCGUGAGCCUUUGGGAC	335
150H5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGAC	336
151I5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGCC	337
152J5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGAU	338
153K5	CGUAAAGGCUCACGCUGACAA	211	UUGUCAGCGUGAGCCUUUACGAC	339
154L5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGUC	340
155M5	CUUAAAGGCUCACGCUGACAA	200	UUGUCAGCGUGAGCCUUUAAGUU	341
156N5	CGGAAAGGCUCACGCUGACAA	212	UUGUCAGCGUGAGCCUUUCCGAC	342
157O5	UUAAAGGCUCACGCUGACAAA	213	UUUGUCAGCGUGAGCCUUUAAGA	343
158P5	AGGCUCACGCUGACAAGCAGA	214	UCUGCUUGUCAGCGUGAGCCUUU	344
159Q5	UGCAGCGGCAGAGGCGGGAGA	215	UCUCCCGCCUCUGCCGCUGCAG	345
160R5	GCGGCAGAGGCGGGAGAUUGU	216	ACCAUCUCCCGCCUCUGCCGCUG	346
161S5	GAGGCGGGAGAUUGGUGGCACA	217	UGUGCCACCAUCUCCCGCCUCUG	347
162T5	GCGGGAGAUUGGUGGCACAGCA	218	UGCUGUGCCACCAUCUCCCGCCU	348
163U5	GUGGCACAGCAGCAUCGGCUA	219	UAGCCGAUGCUGCUGUGCCACCA	349
164V5	CAGCAGCAUCGGCUGCGACAA	220	UUGUCGCAGCCGAUGCUGCUGUG	350
165W5	AGCAGCAUCGGCUGCGACAGA	221	UCUGUCGCAGCCGAUGCUGCUGU	351
166X5	GCAGCAUCGGCUGCGACAGAA	222	UUCUGUCGCAGCCGAUGCUGCUG	352
167Y5	CAGCAUCGGCUGCGACAGAUUA	223	UAUCUGUCGCAGCCGAUGCUGCU	353
168Z5	AGCAUCGGCUGCGACAGAUCA	224	UGAUCUGUCGCAGCCGAUGCUGC	354
169a6	GCAUCGGCUGCGACAGAUCCA	225	UGGAUCUGUCGCAGCCGAUGCUG	355
170b6	CAUCGGCUGCGACAGAUCCAA	226	UUGGAUCUGUCGCAGCCGAUGCUG	356
171c6	UCGGCUGCGACAGAUCCAGGA	227	UCCUGGAUCUGUCGCAGCCGAUG	357
172d6	GGCUGCGACAGAUCCAGGAGA	228	UCUCCUGGAUCUGUCGCAGCCGA	358
173e6	GCUGCGACAGAUCCAGGAGAA	229	UUCUCCUGGAUCUGUCGCAGCCG	359
174e7	CUGCGACAGAUCCAGGAGAGA	230	UCUCUCCUGGAUCUGUCGCAGCC	360

What is Claimed is

1. An RNA interference (RNAi) agent comprising a delivery moiety of Formula I:

5



Formula I,

wherein R comprises a sense strand and an antisense strand,

- 10 wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525, and wherein the sense strand and the antisense strand form a region of complementarity of at least 15 nucleotides, and wherein the sense strand and antisense strand are each independently 18 to 23 nucleotides in length, and optionally wherein the sense strand and antisense strand each independently comprise one or more modified nucleotides, and optionally wherein the sense strand and the antisense strand each independently comprise one or more modified internucleotide linkages, and wherein R is optionally conjugated to Formula I via a linker.

- 20 2. The RNAi agent of claim 1, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405-525.

3. The RNAi agent of claim 1 or 2, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 405, 408, 412, 413, 414, 415, 418, 420, 425, 426, 428, 429, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 448, 449, 451, 452, 454, 457, 458, 459, 463, 464, 465, 466, 467, 468, 469, 471, 472, 473, 474, 475, 476, 479, 490, 491, 492, 493, 495, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, and 509.
4. The RNAi agent of any one of claims 1 to 3, wherein the antisense strand is 23 nucleotides in length.
5. The RNAi agent of any one of claims 1 to 4, wherein the sense strand is 21 nucleotides in length.
6. The RNAi agent of any one of claims 1 to 5, wherein the antisense strand is selected from the group consisting of SEQ ID NOs: 231-361, or a sequence having at least 90% sequence identity thereto.
7. The RNAi agent of any one of claims 1 to 6, wherein the sense strand is selected from the group consisting of SEQ ID NOs: 124-230, or a sequence having at least 90% sequence identity thereto.
8. The RNAi agent of any one of claims 1 to 7, wherein, in the region of complementarity comprises 0, 1, 2, or 3 mismatches between the sense strand and the antisense strand.
9. The RNAi agent of any one of claims 1 to 8, wherein the sense strand and the antisense strand each independently comprise one or more modified nucleotides and the one or more modified nucleotides are independently 2' fluoro modified nucleotides or 2'-O-methyl modified nucleotides.

10. The RNAi agent of any one of claims 1 to 9, wherein each nucleotide of the sense strand and each nucleotide of the antisense strand is a modified nucleotide.
- 5 11. The RNAi agent of any one of claims 1 to 10, wherein the sense strand and antisense strand each independently comprise one or more modified internucleotide linkages, and wherein each modified internucleotide linkage is a phosphorothioate linkage.
12. The RNAi agent of claim 11, wherein the sense strand and antisense strand each independently comprise four phosphorothioate linkages.
- 10 13. The RNAi agent of any one of claims 1 to 12, wherein the 5' nucleotide of the antisense strand comprises a phosphate group or a phosphate analog.
14. The RNAi agent of any one of claims 1 to 13, wherein the antisense strand
15 comprises a sequence selected from the group consisting of SEQ ID NOs: 367-372 and 389-404, or a sequence having at least 90% sequence identity thereto.
15. The RNAi agent of any one of claims 1 to 13, wherein the sense strand comprises a
20 sequence selected from the group consisting of SEQ ID NOs: 361-366 and 373-388, or a sequence having at least 90% sequence identity thereto.
16. The RNAi agent of any one of claims 1 to 15, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
- 25 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto;
- b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 90% sequence identity thereto, and the antisense

- strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 90% sequence identity thereto;
- 5 c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 90% sequence identity thereto;
- d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 90% sequence identity thereto;
- 10 e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto;
- 15 f. a sense strand having the sequence set forth in SEQ ID NO:366, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:372, or a sequence having at least 90% sequence identity thereto;
- g. a sense strand having the sequence set forth in SEQ ID NO:373, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 90% sequence identity thereto;
- 20 h. a sense strand having the sequence set forth in SEQ ID NO:374, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO: 390 or a sequence having at least 90% sequence identity thereto;
- 25 i. a sense strand having the sequence set forth in SEQ ID NO:375, or a sequence having at least 90% sequence identity thereto, and an antisense

- strand having the sequence set forth in SEQ ID NO:391, or a sequence having at least 90% sequence identity thereto;
- 5 j. a sense strand having the sequence set forth in SEQ ID NO:376, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:392, or a sequence having at least 90% sequence identity thereto;
- 10 k. a sense strand having the sequence set forth in SEQ ID NO:377, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:393, or a sequence having at least 90% sequence identity thereto;
- 15 l. a sense strand having the sequence set forth in SEQ ID NO:378, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:394, or a sequence having at least 90% sequence identity thereto;
- 20 m. a sense strand having the sequence set forth in SEQ ID NO:379, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:395, or a sequence having at least 90% sequence identity thereto;
- n. a sense strand having the sequence set forth in SEQ ID NO:380 or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 90% sequence identity thereto;
- 25 o. a sense strand having the sequence set forth in SEQ ID NO: 381, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 90% sequence identity thereto;
- p. a sense strand having the sequence set forth in SEQ ID NO:382, or a sequence having at least 90% sequence identity thereto, and an antisense

- strand having the sequence set forth in SEQ ID NO:397, or a sequence having at least 90% sequence identity thereto;
- 5 q. a sense strand having the sequence set forth in SEQ ID NO:383, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:398, or a sequence having at least 90% sequence identity thereto;
- 10 r. a sense strand having the sequence set forth in SEQ ID NO:384, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:399, or a sequence having at least 90% sequence identity thereto;
- s. a sense strand having the sequence set forth in SEQ ID NO:385, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:400, or a sequence having at least 90% sequence identity thereto;
- 15 t. a sense strand having the sequence set forth in SEQ ID NO:386, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:401, or a sequence having at least 90% sequence identity thereto;
- 20 u. a sense strand having the sequence set forth in SEQ ID NO:387, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:402, or a sequence having at least 90% sequence identity thereto;
- v. a sense strand having the sequence set forth in SEQ ID NO:388, or a sequence having at least 90% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:403, or a sequence having at least 90% sequence identity thereto; and
- 25 w. a sense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 90% sequence identity thereto, and an antisense

strand having the sequence set forth in SEQ ID NO:404, or a sequence having at least 90% sequence identity thereto.

17. The RNAi agent of any one of claims 1 to 16, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
- 5 a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto;
 - 10 b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 95% sequence identity thereto;
 - 15 c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 95% sequence identity thereto;
 - 20 d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 95% sequence identity thereto;
 - 25 e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto;
 - f. a sense strand having the sequence set forth in SEQ ID NO:366, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:372, or a sequence having at least 95% sequence identity thereto;

- g. a sense strand having the sequence set forth in SEQ ID NO:373, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:389, or a sequence having at least 95% sequence identity thereto;
- 5 h. a sense strand having the sequence set forth in SEQ ID NO:374, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO: 390 or a sequence having at least 95% sequence identity thereto;
- 10 i. a sense strand having the sequence set forth in SEQ ID NO:375, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:391, or a sequence having at least 95% sequence identity thereto;
- 15 j. a sense strand having the sequence set forth in SEQ ID NO:376, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:392, or a sequence having at least 95% sequence identity thereto;
- 20 k. a sense strand having the sequence set forth in SEQ ID NO:377, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:393, or a sequence having at least 95% sequence identity thereto;
- l. a sense strand having the sequence set forth in SEQ ID NO:378, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:394, or a sequence having at least 95% sequence identity thereto;
- 25 m. a sense strand having the sequence set forth in SEQ ID NO:379, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:395, or a sequence having at least 95% sequence identity thereto;

- n. a sense strand having the sequence set forth in SEQ ID NO:380 or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 95% sequence identity thereto;
- 5 o. a sense strand having the sequence set forth in SEQ ID NO: 381, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:396, or a sequence having at least 95% sequence identity thereto;
- 10 p. a sense strand having the sequence set forth in SEQ ID NO:382, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:397, or a sequence having at least 95% sequence identity thereto;
- 15 q. a sense strand having the sequence set forth in SEQ ID NO:383, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:398, or a sequence having at least 95% sequence identity thereto;
- 20 r. a sense strand having the sequence set forth in SEQ ID NO:384, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:399, or a sequence having at least 95% sequence identity thereto;
- s. a sense strand having the sequence set forth in SEQ ID NO:385, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:400, or a sequence having at least 95% sequence identity thereto;
- 25 t. a sense strand having the sequence set forth in SEQ ID NO:386, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:401, or a sequence having at least 95% sequence identity thereto;

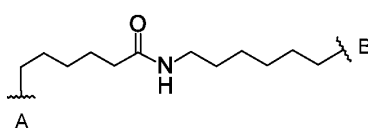
- u. a sense strand having the sequence set forth in SEQ ID NO:387, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:402, or a sequence having at least 95% sequence identity thereto;
 - 5 v. a sense strand having the sequence set forth in SEQ ID NO:388, or a sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:403, or a sequence having at least 95% sequence identity thereto; and
 - w. a sense strand having the sequence set forth in SEQ ID NO:389, or a
10 sequence having at least 95% sequence identity thereto, and an antisense strand having the sequence set forth in SEQ ID NO:404, or a sequence having at least 95% sequence identity thereto.
18. The RNAi agent of any one of claims 1-16, wherein the sense strand and antisense
15 strand are a pair of oligonucleotide sequences selected from the group consisting of:
- a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto;
 - 20 b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 90% sequence identity thereto;
 - c. a sense strand having the sequence set forth in SEQ ID NO:363, or a
25 sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 90% sequence identity thereto;
 - d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 90% sequence identity thereto, and the antisense

- strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 90% sequence identity thereto; and
- 5 e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto.
19. The RNAi agent of any one claims 1 to 16 or claim 18, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group
- 10 consisting of:
- a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 95% sequence identity thereto;
- 15 b. a sense strand having the sequence set forth in SEQ ID NO:362, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:368, or a sequence having at least 95% sequence identity thereto;
- c. a sense strand having the sequence set forth in SEQ ID NO:363, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:369, or a sequence having at least 95% sequence identity thereto;
- 20 d. a sense strand having the sequence set forth in SEQ ID NO:364, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:370, or a sequence having at least 95% sequence identity thereto; and
- 25 e. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense

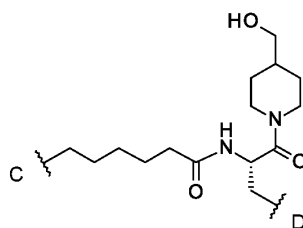
strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 95% sequence identity thereto.

- 5 20. The RNAi agent of any one of claims 1 to 18, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
- a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence having at least 90% sequence identity thereto; and
 - 10 b. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 90% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence having at least 90% sequence identity thereto.
- 15 21. The RNAi agent of any one of claims 1 to 20, wherein the sense strand and antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:
- a. a sense strand having the sequence set forth in SEQ ID NO:361, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:367, or a sequence
 - 20 having at least 95% sequence identity thereto; and
 - b. a sense strand having the sequence set forth in SEQ ID NO:365, or a sequence having at least 95% sequence identity thereto, and the antisense strand having the sequence set forth in SEQ ID NO:371, or a sequence
 - 25 having at least 95% sequence identity thereto.
22. The RNAi agent of any one of the claims 1 to 21, wherein R is conjugated to Formula I via a linker.

23. The RNAi agent of claim 22, wherein R is conjugated to Formula I via a linker, and wherein linker comprises a linker of Formula II having connection points A and B or the linker comprises Formula III having connection points C and D, and wherein connection point A or connection point C is conjugated to Formula I and connection point B or connection point D is conjugated to a phosphate group which is conjugated to R;

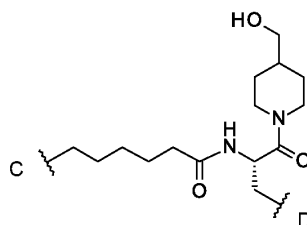


Formula II;



Formula III.

24. The RNAi agent of any one of claims 1 to 23, wherein R is conjugated to Formula I via a linker, and wherein the linker is a linker comprising Formula III having connection points C and D, and wherein connection point C is conjugated to Formula I and connection point D is conjugated to a phosphate group which is conjugated to R;



Formula III.

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25. The RNAi agent of any one of claims 1 to 24, wherein the sense strand and the antisense strand are a pair of oligonucleotide sequences selected from the group consisting of:

- 10 a. a sense strand consisting of the sequence set forth in SEQ ID NO:361 and an antisense strand consisting of the sequence set forth in SEQ ID NO:367; and
- b. a sense strand consisting of the sequence set forth in SEQ ID NO:365 and an antisense strand consisting of the sequence set forth in SEQ ID NO:371,

15 26. The RNAi agent of any one of claims 1 to 25, wherein the RNAi agent is capable of decreasing expression of the ANGPTL8 gene in a liver cell.

27. The RNAi agent of any one of claims 1 to 26, for use in therapy.

20 28. The RNAi agent of any one of claims 1 to 26, for use in the treatment of dyslipidemia.

29. A pharmaceutical composition comprising the RNAi agent of any one of claims 1-26, and one or more pharmaceutically acceptable excipients.

30. The use of the RNAi agent of any one of claims 1-26, for the manufacture of a medicament for the treatment of dyslipidemia.
31. A method of treating dyslipidemia in a patient in need thereof, comprising
5 administering the RNAi agent of any one of claims 1 to 26, or a pharmaceutical composition thereof.
32. A method of decreasing ANGPTL8 expression in a cell, comprising contacting the cell with the RNAi agent of any one of claims 1 to 26, and incubating the cell for a
10 time sufficient for decreasing the level of ANGPTL8 mRNA by at least 50% as compared to an untreated or control treated cell.

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