

[006] ANGPTL3 is a member of the angiopoietin-like family of secreted proteins that regulates lipid metabolism and that is primarily expressed in the liver (Koishi *et al.* (2002) *Nat. Genet.* 30:151-157). ANGPTL3 inhibits lipoprotein lipase (LPL), which catalyzes the hydrolysis of triglycerides, and inhibits endothelial lipase (EL), which hydrolyzes high density lipoprotein (HDL) phospholipids.

~~BRIEF~~ SUMMARY

[007] ~~Aspects~~ Examples of the disclosure relate to compositions and methods for treating a disease, disorder and/or condition related to ANGPTL3 expression. The disclosure is based, in part, on the discovery and development of oligonucleotides that selectively inhibit and/or reduce ANGPTL3 expression.

[008] In some embodimentexamples, the disclosure provides an oligonucleotide for reducing ANGPTL3 expression, where the oligonucleotide comprises an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116.

[009] In some embodimentexamples, the disclosure provides an oligonucleotide for reducing ANGPTL3 expression, where the oligonucleotide comprises a sense strand comprising a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115.

[0010] In some embodimentexamples, the oligonucleotide for reducing ANGPTL3 expression comprises an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, where the antisense strand has a region of complementarity to a target sequence of ANGPTL3 as set forth in any one of SEQ ID NOs: 125, 126, 127, 118, 119, 120, 121, 122, 123, 124, and 117, and where the region of complementarity is at least 15 contiguous nucleotides in length.

[0011] In some embodimentexamples, the antisense strand is 19 to 27 nucleotides in length or 21 to 27 nucleotides in length. In some embodimentexamples, the antisense strand is 22 nucleotides in length.

[0012] In some embodimentexamples, the sense strand is 19 to 40 nucleotides in length. In some embodimentexamples, the sense strand is 36 nucleotides in length.

[0013] In some embodimentexamples, the oligonucleotide for reducing ANGPTL3 expression has a duplex region of at least 19 nucleotides in length or at least 21 nucleotides in length. In some embodimentexamples, the duplex region is 20 nucleotides in length.

[0014] In some [embodimentexamples](#), the region of complementarity to ANGPTL3 is at least 19 contiguous nucleotides in length or at least 21 contiguous nucleotides in length.

[0015] In some [embodimentexamples](#), the oligonucleotide for reducing ANGPTL3 expression comprises on the sense strand at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and where L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

[0016] In some [embodimentexamples](#), an oligonucleotide for reducing ANGPTL3 expression comprises an antisense strand and a sense strand, where the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to ANGPTL3, where the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, where S1 is complementary to S2, where L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and where the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length but are not covalently linked.

[0017] In some [embodimentexamples](#), the loop L is a tetraloop. In some [embodimentexamples](#), L is 4 nucleotides in length. In some [embodimentexamples](#), L comprises a sequence GAAA.

[0018] In some [embodimentexamples](#), the oligonucleotide for reducing ANGPTL3 expression comprises an antisense strand that is 27 nucleotides in length and a sense strand that is 25 nucleotides in length. In some [embodimentexamples](#), the oligonucleotide comprises an antisense strand that is 22 nucleotides in length and a sense strand that is 36 nucleotides in length.

[0019] In some [embodimentexamples](#), an oligonucleotide with a duplex region comprises a 3'-overhang sequence on the antisense strand. In some [embodimentexamples](#), the 3'-overhang sequence on the antisense strand is 2 nucleotides in length.

[0020] In some [embodimentexamples](#), the oligonucleotide for reducing ANGPTL3 expression comprises an antisense strand and a sense strand that are each in a range of 21 to 23 nucleotides in length. In some [embodimentexamples](#), the oligonucleotide comprises a duplex structure in a range of 19 to 21 nucleotides in length. In some such [embodimentexamples](#), the oligonucleotide comprises a 3'-overhang sequence of one or more nucleotides in length, where the 3'-overhang sequence is present on the antisense strand, the sense strand, or the antisense strand and sense strand. In some [embodimentexamples](#), the 3'-overhang sequence of 2 nucleotides in length, where the 3'-overhang sequence is on the antisense strand, and where the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length, such that the sense strand and antisense strand form a duplex of 21 nucleotides in length.

[0021] In some [embodimentexamples](#), the oligonucleotide for reducing ANGPTL3 expression comprises at least one modified nucleotide. In some [embodimentexamples](#), the modified nucleotide

comprises a 2'-modification. In some [embodimentexamples](#), all of the nucleotides of the oligonucleotide are modified, for example with a 2'-modification.

[0022] In some [embodimentexamples](#), the oligonucleotide for reducing ANGPTL3 expression comprises at least one modified internucleotide linkage, preferably a phosphorothioate linkage.

[0023] In some [embodimentexamples](#), the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, for example, an oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

[0024] In some [embodimentexamples](#), at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands, such as a carbohydrate, amino sugar, cholesterol, polypeptide or lipid. In some [embodimentexamples](#), the targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety. In some [embodimentexamples](#), the GalNAc moiety comprises a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

[0025] In some [embodimentexamples](#), the targeting ligand is conjugated to one or more nucleotides of L of the stem-loop. In some [embodimentexamples](#), up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

[0026] In some [embodimentexamples](#), the oligonucleotide for reducing ANGPTL3 expression is an RNAi oligonucleotide.

[0027] In another [aspectexample](#), the disclosure provides a method of reducing ANGPTL3 expression in a cell, a population of cells or a subject by administering an oligonucleotide herein. In some [embodimentexamples](#), a method of for reducing ANGPTL3 expression in a cell, a population of cells or a subject comprises a step of contacting the cell or the population of cells or administering to the subject an effective amount of an oligonucleotide herein, or a pharmaceutical composition thereof. In some [embodimentexamples](#), the method for reducing ANGPTL3 expression comprises reducing an amount or a level of ANGPTL3 mRNA, an amount or a level of ANGPTL3 protein, or both.

[0028] In some [embodimentexamples](#), the disclosure provides a method for reducing an amount or level of triglyceride (TG) in a subject by administering to the subject an effective amount of an oligonucleotide herein, or a pharmaceutical composition thereof.

[0029] In some [embodimentexamples](#), the disclosure provides a method for reducing an amount or level of cholesterol in a subject by administering to the subject an effective amount of the oligonucleotide herein, or a pharmaceutical composition thereof.

[0030] In some [embodimentexamples](#), a subject for treatment with an oligonucleotide herein has a disease, disorder or condition associated with ANGPTL3 expression. In some [embodimentexamples](#),

a method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression comprises administering to the subject in need thereof a therapeutically effective amount of an oligonucleotide herein, or a pharmaceutical composition thereof, thereby treating the subject.

[0031] In some [embodimentexamples](#), an oligonucleotide herein for administration comprises a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, where the sense strand forms a duplex region with the antisense strand, where the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115, and where the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116, or pharmaceutical composition thereof, thereby treating the subject.

[0032] In some [embodimentexamples](#), a method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression comprises administering to the subject in need thereof a therapeutically effective amount of an oligonucleotide comprising a pair of sense and antisense strands selected from a row of the table set forth in Table 5, or pharmaceutical composition thereof, thereby treating the subject.

[0033] In some [embodimentexamples](#), the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.

[0034] In some [embodimentexamples](#), the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[0035] In some [embodimentexamples](#), the oligonucleotide, or pharmaceutical composition thereof, is administered in combination with a second therapeutic agent or composition thereof.

[0036] In a further [aspectexample](#), the present disclosure provides use of any of the oligonucleotides of the present disclosure, or the pharmaceutical composition thereof, in the manufacture of a

medicament for the treatment of a disease, disorder or condition associated with ANGPTL3 expression.

[0037] In some [embodimentexamples](#), the oligonucleotide of the disclosure, or the pharmaceutical composition of the disclosure, is for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with ANGPTL3 expression.

[0038] In a further [aspectexample](#), the oligonucleotide of the present disclosure is provided in the form of a kit for treating a disease, disorder or condition associated with ANGPTL3 expression. In some [embodimentexamples](#), the kit comprises an oligonucleotide herein, and a pharmaceutically acceptable carrier. In some [embodimentexamples](#), the kit further includes a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.

[0039] In some [embodimentexamples](#) of the use or kits, the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, NASH, NAFLD, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.

[0040] In some [embodimentexamples](#) of the use or kits, the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[\[0040a\] In one aspect, the present disclosure refers to an oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116, optionally wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114.](#)

[\[0040b\] In another aspect, the present disclosure refers to an oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the antisense strand has a region of complementarity to a target sequence of ANGPTL3 as set forth in any one of SEQ ID NOs: 125, 126, 127, 118, 119, 120, 121, 122, 123, 124, and 117, and wherein the region of complementarity is at least 15 contiguous nucleotides in length, optionally:](#)

wherein the region of complementarity is fully complementary to the target sequence of ANGPTL3; and/or wherein the sense strand forms a duplex region with the antisense strand.

[0040c] In another aspect, the present disclosure an oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to ANGPTL3, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length but are not covalently linked, optionally wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of ANGPTL3 mRNA; and/or optionally wherein the oligonucleotide comprises a 3'-overhang sequence on the antisense strand of 2 nucleotides in length.

[0040d] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the oligonucleotide in the disclosure and a pharmaceutically acceptable carrier, delivery agent or excipient.

[0040e] In yet another aspect, the present disclosure refers to an *in vitro* method for reducing ANGPTL3 expression in a cell or a population of cells wherein the method comprises: contacting the cell or the population of cells with the oligonucleotide in the disclosure or the pharmaceutical composition in the disclosure, wherein reducing ANGPTL3 expression comprises reducing an amount or a level of ANGPTL3 mRNA, an amount or a level of ANGPTL3 protein, or both.

[0040f] In yet another aspect, the present disclosure refers to use of the oligonucleotide in the disclosure or the pharmaceutical composition in the disclosure, in the manufacture of a medicament for treating a disease, selected from a group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia, optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[0040g] In yet another aspect, the present disclosure refers to use of an oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5,

7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115, and wherein the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116, or pharmaceutical composition thereof, in the manufacture of a medicament thereby for treating a disease, selected from a group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia, optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[0040h] In yet another aspect, the present disclosure refers to use of an oligonucleotide comprising a pair of sense and antisense strands selected from a row set forth in Table 5 of the disclosure, or pharmaceutical composition thereof, in the manufacture of a medicament thereby for treating a disease, selected from a group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia, optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[0040i] In yet another aspect, the present disclosure refers to a kit comprising the oligonucleotide of the disclosure, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] FIG. 1 provides a graph depicting the percent (%) of ANGPTL3 mRNA in HuH-7 cells transfected with the indicated DsiRNAs relative to the % of ANGPTL3 mRNA control mock-treated cells.

[0042] FIG. 2 provides a graph depicting the percent (%) of ANGPTL3 mRNA in HuH-7 cells transfected with the indicated DsiRNAs relative to the % of ANGPTL3 mRNA control mock-treated cells.

[0043] FIG. 3 provides a schematic depicting the structure and chemical modification patterns of generic GalNAc-conjugated ANGPTL3 oligonucleotides.

[0044] FIG. 4 provides a graph depicting the percent (%) of ANGPTL3 mRNA in liver samples from mice treated with the indicated GalNAc-conjugated ANGPTL3 oligonucleotides relative to mice treated with phosphate buffered saline (PBS).

CLAIMS

What is claimed is:

1. An oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116, optionally wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114.

2. The oligonucleotide of claim 1, comprising a sense strand comprising a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115, optionally wherein sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 99, 101, 103, 19, 25, 49, 71, 73, 75, 79, and 113; optionally wherein the sense strand forms a duplex region with the antisense strand.

~~3. The oligonucleotide of claim 1 or 2, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114.~~

~~4. The oligonucleotide of claim 2 or 3, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 99, 101, 103, 19, 25, 49, 71, 73, 75, 79, and 113.~~

~~5.~~ 53. An oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the antisense strand has a region of complementarity to a target sequence of ANGPTL3 as set forth in any one of SEQ ID NOs: 125, 126, 127, 118, 119, 120, 121, 122, 123, 124, and 117, and wherein the region of complementarity is at least 15 contiguous nucleotides in length, optionally:-

~~6. The oligonucleotide of claim 5, wherein the region of complementarity is fully complementary to the target sequence of ANGPTL3; and/or~~
wherein the sense strand forms a duplex region with the antisense strand.

~~74.~~ The oligonucleotide of any one of claims 1 to ~~63~~, wherein the antisense strand is 19 to 27 nucleotides in length~~;~~

~~8.~~ ~~The oligonucleotide of any one of claims 1 to 7, optionally~~ wherein the antisense strand is 21 to 27 nucleotides in length, further optionally wherein the antisense strand is 22 nucleotides in length; and/or

~~9.~~ ~~The oligonucleotide of any one of claims 2 to 8, wherein the sense strand forms a duplex region with the antisense strand.~~

~~10.~~ ~~The oligonucleotide of claim 9,~~ wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.

~~11.~~ The oligonucleotide of any one of claims 2 to 4, 9 or 10, wherein the duplex region is at least 19 nucleotides in length~~;~~

~~12.~~ ~~The oligonucleotide of any one of claims 9 to 11,~~
optionally wherein the duplex region is at least 21 nucleotides in length, further optionally wherein the duplex region is 20 nucleotides in length; and/or

~~13.~~ ~~The oligonucleotide of any one of claims 5 to 12,~~ wherein the region of complementarity to ANGPTL3 is at least 19 contiguous nucleotides in length~~;~~

~~14.~~ ~~The oligonucleotide of any one of claims 5 to 13,~~
optionally wherein the region of complementarity to ANGPTL3 is at least 21 contiguous nucleotides in length.

~~15.~~ The oligonucleotide of any one of claims ~~5 to 14~~ 3 to 5, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116~~;~~

optionally wherein the antisense strand comprises a sequence as set forth in any one of

SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114; and/or -

~~16. The oligonucleotide of any one of claims 5 to 15,~~ wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115₂.

optionally -

~~17. The oligonucleotide of any one of claims 5 to 16, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 100, 102, 104, 20, 26, 50, 72, 74, 76, 80, and 114.~~

~~18. The oligonucleotide of any one of claims 5 to 17,~~ wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 99, 101, 103, 19, 25, 49, 71, 73, 75, 79, and 113.

~~197.~~ The oligonucleotide of any one of claims 2 to ~~18~~6, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

~~208.~~ An oligonucleotide for reducing ANGPTL3 expression, the oligonucleotide comprising an antisense strand and a sense strand,

wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to ANGPTL3, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and

wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length but are not covalently linked~~-~~

~~21. The oligonucleotide of claim 20,~~

optionally wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of ANGPTL3 mRNA; and/or

optionally wherein the oligonucleotide comprises a 3'-overhang sequence on the antisense strand of 2 nucleotides in length.

~~229.~~ The oligonucleotide of ~~any one of~~ claims ~~7 or 8-19 to 21~~, wherein L is a tetraloop.

~~23.~~ The oligonucleotide of ~~any one of~~ claims ~~19 to 22~~,
~~optionally~~ wherein L is 4 nucleotides in length.

~~24.~~ The oligonucleotide of ~~any one of~~ claims ~~19 to 23~~,
~~further optionally~~ wherein L comprises a sequence set forth as GAAA.

~~2510.~~ The oligonucleotide of any one of claims ~~3 to 95 to 24~~, wherein the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length, ~~optionally or~~ wherein the antisense strand is 22 nucleotides in length and the sense strand is 36 nucleotides in length.

~~26.~~ The oligonucleotide of claim ~~25~~,
~~optionally~~ wherein the antisense strand and sense strand form a duplex region of 25 nucleotides in length, ~~optionally wherein the duplex is or~~ 20 nucleotides in length.

~~27.~~ The oligonucleotide of any one of claims ~~20 to 24~~, comprising a 3'-overhang sequence on the antisense strand of 2 nucleotides in length.

~~2811.~~ The oligonucleotide of ~~any one of~~ claims ~~2 to 69 to 18~~, wherein the oligonucleotide comprises an antisense strand and a sense strand that are each in a range of 21 to 23 nucleotides in length.

~~29.~~ The oligonucleotide of claim ~~28~~,
~~optionally~~ wherein the oligonucleotide comprises a duplex structure in a range of 19 to 21 nucleotides in length.

~~30.~~ The oligonucleotide of claim ~~28 or 29~~,
~~further optionally:~~ wherein the oligonucleotide comprises a 3'-overhang sequence of one or more nucleotides in length, wherein the 3'-overhang sequence is present on the antisense strand, the sense strand, or the antisense strand and sense strand.

~~31.~~ The oligonucleotide of claim ~~28 or 29~~;

~~or~~ wherein the oligonucleotide comprises a 3'-overhang sequence of 2 nucleotides in length, wherein the 3'-overhang sequence is on the antisense strand, and wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length, such that the sense strand and antisense strand form a duplex of 21 nucleotides in length.

~~32~~12. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide, or all of the nucleotides of the oligonucleotide are modified, -

~~33. — The oligonucleotide of claim 32, optionally~~ wherein the modified nucleotide comprises a 2'-modification-

~~34. — The oligonucleotide of claim 33,~~
 further optionally wherein the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid.

~~35. — The oligonucleotide of any one of claims 32 to 34, wherein all of the nucleotides of the oligonucleotide are modified.~~

~~36~~13. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage-

~~37. — The oligonucleotide of claim 36,~~
 optionally wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

~~38~~14. The oligonucleotide of any one of the preceding claims, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog-

~~39. — The oligonucleotide of claim 38,~~
 optionally wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

~~40~~15. The oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.

~~41.~~ ~~The oligonucleotide of claim 40,~~
~~_____ optionally~~ wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid.

~~42.~~ ~~The oligonucleotide of claim 40,~~
~~_____ further optionally~~ wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.

~~43.~~ ~~The oligonucleotide of claim 42,~~
~~_____ further optionally~~ wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.

~~44.~~16. The oligonucleotide of any one of claims ~~7 to 9~~19 to 24, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

~~45~~17. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide is an RNAi oligonucleotide.

~~46~~18. A pharmaceutical composition comprising the oligonucleotide of any one of the preceding claims and a pharmaceutically acceptable carrier, delivery agent or excipient.

~~47.~~ ~~A method of delivering an oligonucleotide to a subject, the method comprising administering pharmaceutical composition of claim 46 to the subject.~~

~~48~~19. An *in vitro* method for reducing ANGPTL3 expression in a cell ~~, or~~ a population of cells ~~or a subject, wherein~~ the method comprises ~~the step of~~:

~~_____ i. _____~~ contacting the cell or the population of cells with the oligonucleotide of any one of claims ~~1 to 45~~1 to 17, or the pharmaceutical composition of claim ~~46; or~~18

~~_____ ii. _____~~ administering to the subject the oligonucleotide of any one of claims ~~1 to 45, or the pharmaceutical composition of claim 46.~~

~~49.—The method of claim 48,~~

~~_____ wherein reducing ANGPTL3 expression comprises reducing an amount or a level of ANGPTL3 mRNA, an amount or a level of ANGPTL3 protein, or both.~~

~~5020.—A method for reducing an amount or level of triglyceride (TG) in a subject, the method comprising administering to the subject _____ Use of the oligonucleotide of any one of claims 1 to 1745, or the pharmaceutical composition of claim 18, 46, in the manufacture of a medicament for treating a disease, selected from a group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia,~~

~~_____ optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.~~

~~51.—A method for reducing an amount or level of cholesterol in a subject, the method comprising administering to the subject the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46.~~

~~52.—The method of any one of claims 48 to 51, wherein the subject has a disease, disorder or condition associated with ANGPTL3 expression.~~

~~53.—A method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression, the method comprising administering to the subject a therapeutically effective amount of the oligonucleotide of any one of claims 1 to 45, or the pharmaceutical composition of claim 46, thereby treating the subject.~~

~~54.21. A method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression, the method comprising administering to the subject a therapeutically effective amount of Use of an oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31,~~

33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, and 115, and wherein the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, and 116, or pharmaceutical composition thereof, ~~thereby treating the subject, in the manufacture of a medicament thereby for treating a disease, selected from a group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia,~~

optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

~~55.22. A method for treating a subject having a disease, disorder or condition associated with ANGPTL3 expression, the method comprising administering to the subject a therapeutically effective amount of~~ Use of an oligonucleotide comprising a pair of sense and antisense strands selected from a row set forth in Table 5, or pharmaceutical composition thereof, ~~thereby treating the subject, in the manufacture of a medicament thereby for treating a disease, selected from a group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia,~~

optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

~~56.—The method of any one of claims 52-55, wherein the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-~~

~~alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.~~

~~57. The method of claim 56, wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.~~

~~58~~23. The ~~method~~use of any one of claims ~~53-57~~20 to 22, wherein the oligonucleotide, or pharmaceutical composition, is to be administered in combination with a second composition or therapeutic agent.

~~59. Use of the oligonucleotide of any one of claims 1-45, or the pharmaceutical composition of claim 46, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with ANGPTL3 expression.~~

~~60~~24. The oligonucleotide of any one of claims ~~1 to 17~~4 to 17, or the pharmaceutical composition of claim ~~18~~46, for use as a medicament, ~~or adaptable for use, in the treatment of a disease, disorder or condition associated with ANGPTL3 expression.~~

~~61~~25. A kit comprising the oligonucleotide of any one of claims ~~1-45~~1 to 17, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.

~~62. The use of claim 59, the oligonucleotide or pharmaceutical composition for use of claim 60, or the kit of claim 61, wherein the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.~~

~~63. The use of claim 59, the oligonucleotide or pharmaceutical composition for use of claim 60, or the kit of claim 61, wherein the disease, disorder or condition associated with ANGPTL3~~

expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.