The binding of chylomicrons and VLDL particles to the lipolysis-stimulated receptor (LSR) is also significantly inhibited by APOC3.

An increase in APOC3 levels induces the development of hypertriglyceridemia, or high (hyper-) blood levels (-emia) of triglycerides. Elevated levels of triglycerides are associated with a variety of diseases, including cardiovascular disease, atherosclerosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, polycystic ovary syndrome, kidney disease, obesity, type 2 diabetes mellitus (insulin resistance), hypertension and skin lesions (xanthomas). Very high triglyceride levels also increase the risk of acute pancreatitis. Therefore, regulating APOC3 metabolism is an important therapeutic approach to managing hypertriglyceridemia and the associated diseases.

Accordingly, there is a need in the art for regulators of APOC3 expression for treating apolipoprotein C3-associated disorders, such as hypertriglyceridemia.

Summary of the Invention

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding apolipoprotein C3 (APOC3). The apolipoprotein C3 (APOC3) may be within a cell, *e.g.,* a cell within a subject, such as a human subject.

In one aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from nucleotides; 432-454 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification, wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and wherein at least one strand is conjugated to a ligand.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of CUUAAAAGGGACAGUAUUCUA (SEQ ID NO:13), and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of UAGAAUACUGUCCCUUUUAAGCC (SEQ ID NO:14), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification, wherein both the sense strand and

the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and wherein at least one strand is conjugated to a ligand.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of nucleotides 429-456 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification, wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and wherein at least one strand is conjugated to a ligand.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding APOC3, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-5, 14, and 15.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, (a) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 232-254; 233-255; 238-260; 239-261; 242-264; 243-265; 244-266; 264-286; 268-290; 426-448; 431-453; 432-454; 433-455; 435-457; 436-458; 499-521; 500-522; 503-525; 504-526; 507-529; 510-532; or 511-533 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or (b) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 235-257; 238-260; 242-264; 243-265; 244-266; 426-448; 430-450; 431-453; 432-454; 433-455; 435-457; 436-458; 499-521; 503-525; and 504-526 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or (c) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 232-254; 239-261; 242-264; 244-266; 258-280; 264-286; 268-290, 429-451; 430-450; 430-452; 433-455; 434-456; 435-457; 500-522; 503-525; 507-529; and 510-532 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or (d) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 429-451; 430-452; 431-451; 432-

452; 433-455; 504-526; and 506-526 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or (e) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 429-455 or 504-532 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or (f) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 429-451; 430-452; 431-451; 432-452; 433-455; 434-452; 504-526; and 506-526 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In another aspect, provided herein is a cell containing the dsRNA agent as described herein.

In another aspect, provided herein is a pharmaceutical composition for inhibiting expression of a gene encoding apolipoprotein C3 (APOC3) comprising the dsRNA agent as described herein.

In another aspect, provided herein is an *in vitro* method of inhibiting expression of an apolipoprotein C3 (APOC3) gene in a cell, the method comprising contacting the cell with the dsRNA agent as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression of the APOC3 gene in the cell.

In another aspect, provided herein is use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in apolipoprotein C3 expression.

In another aspect, provided herein is a kit comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In another aspect, provided herein is a vial comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In yet another aspect, provided herein is a syringe comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In yet another aspect, provided herein is the dsRNA agent as described herein, or the pharmaceutical composition as described herein for use in therapy.

In an aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:2. In one embodiment, the dsRNA agent comprises at least one thermally destabilizing nucleotide modification, *e.g.,* an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an

unlocked nucleic acids (UNA), or a glycerol nucleic acid (GNA), *e.g.,* the antisense strand comprises at least one thermally destabilizing nucleotide modification.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of apolipoprotein C3 in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding apolipoprotein C3, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-5, 14, and 15.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of apolipoprotein C3 in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from nucleotides; 432-454 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2,

wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification,

wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and

wherein at least one strand is conjugated to a ligand.

2. The dsRNA agent of claim 1,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5’-CUUAAAAGGGACAGUAUUCUA-3’ (SEQ ID NO:13), and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotide sequence of 5’-UAGAAUACUGUCCCUUUUAAGCC-3’ (SEQ ID NO:14).

3. The dsRNA agent of claim 1 or 2, wherein the sense strand comprises 4 2'-fluoro modified nucleotides at nucleotides 7 and 9-11, counting from the 5’-end, and the antisense strand comprises 2 2'-fluoro modified nucleotides at nucleotides 14 and 16, counting from the 5’-end, and 3 2'-deoxy-modified nucleotides at nucleotides 2, 5, and 7, counting from the 5’-end.

4. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of CUUAAAAGGGACAGUAUUCUA (SEQ ID NO:13), and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of UAGAAUACUGUCCCUUUUAAGCC (SEQ ID NO:14),

wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification,

wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and

wherein at least one strand is conjugated to a ligand.

5. The dsRNA agent of claim 4, wherein the sense strand comprises 2-6 2'-fluoro modified nucleotides.

6. The dsRNA agent of claim 4 or 5, wherein the antisense strand comprises no more than 4 2'-fluoro modified nucleotides.

7. The dsRNA agent of any one of claims 4-6 wherein the antisense strand comprises 1-5 deoxy-modified nucleotides.

8. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of nucleotides 429-456 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2,

wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification,

wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and wherein at least one strand is conjugated to a ligand.

9. The dsRNA agent of any one of claims 4-8, wherein the sense strand comprises 2-6 2'-fluoro modified nucleotides.

10. The dsRNA agent of any one of claims 4-9, wherein the sense strand comprises 4 2'-fluoro modified nucleotides.

11. The dsRNA agent of any one of claims 4-10, wherein the antisense strand comprises 2-4 2'-fluoro modified nucleotides.

12. The dsRNA agent of claim 11, wherein the antisense strand comprises 2 2'-fluoro modified nucleotides.

13. The dsRNA agent of any one of claims 4-12, wherein the antisense strand comprises 1-5 2'-deoxy-modified nucleotides.

14. The dsRNA agent of claim 13, wherein the antisense strand comprises 3 2'-deoxy-modified nucleotides.

15. The dsRNA agent of any one of claims 4-14, wherein the sense strand comprises 4 2'-fluoro modified nucleotides at nucleotides 7 and 9-11, counting from the 5'-end, and the antisense strand comprises 2 2'-fluoro modified nucleotides at nucleotides 14 and 16, counting from the 5'-end, and 3 2'-deoxy-modified nucleotides at nucleotides 2, 5, and 7, counting from the 5'-end.

16. The dsRNA agent of any one of claims 1-15, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5'-terminus.

17. The dsRNA agent of any one of claims 1-16, wherein the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at both the 5'- and the 3'-terminus.

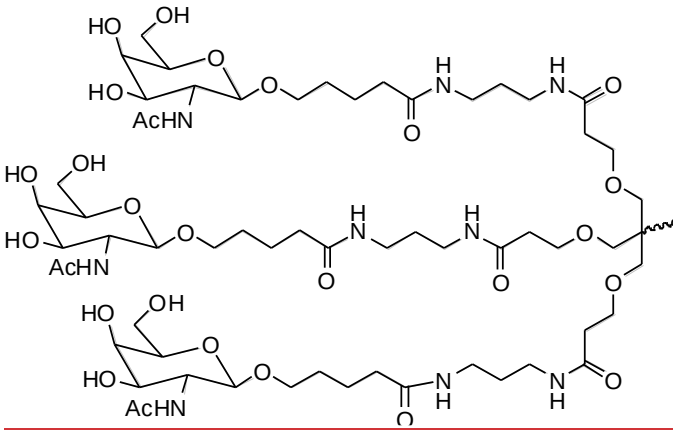
18. The dsRNA agent of any one of claims 1-17, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5'-terminus and the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at both the 5'- and the 3'-terminus.

19. The dsRNA agent of any one of claims 1-18, wherein the ligand is conjugated to the 3'-end of the sense strand.

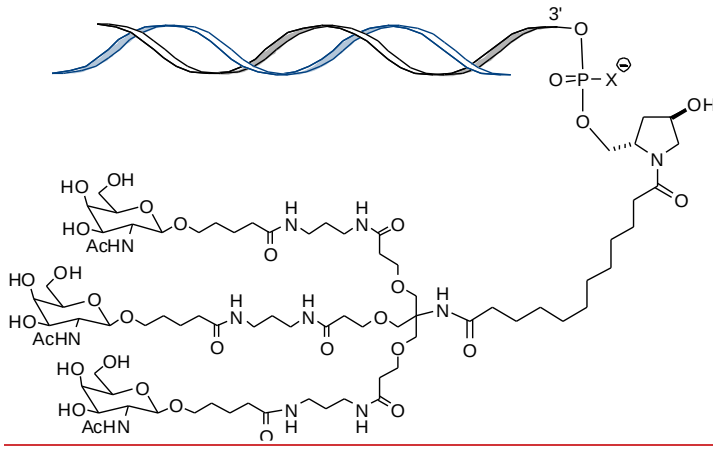
20. The dsRNA agent of any one of claims 1-19, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

21. The dsRNA agent of claim 20, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

22. The dsRNA agent of claim 21, wherein the ligand is



23. The dsRNA agent of claim 22, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O.

24~~1~~. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding APOC3, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-5, 14, and 15.

25~~2~~. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell,

wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

(a) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 232-254; 233-

255; 238-260; 239-261; 242-264; 243-265; 244-266; 264-286; 268-290; 426-448; 431-453; 432-454; 433-455; 435-457; 436-458; 499-521; 500-522; 503-525; 504-526; 507-529; 510-532; or 511-533 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or

(b) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 235-257; 238-260; 242-264; 243-265; 244-266; 426-448; 430-450; 431-453; 432-454; 433-455; 435-457; 436-458; 499-521; 503-525; and 504-526 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or

(c) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 232-254; 239-261; 242-264; 244-266; 258-280; 264-286; 268-290, 429-451; 430-450; 430-452; 433-455; 434-456; 435-457; 500-522; 503-525; 507-529; and 510-532 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or

(d) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 429-451; 430-452; 431-451; 432-452; 433-455; 504-526; and 506-526 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or

(e) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 429-455 or 504-532 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; or

(f) wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 429-451; 430-452; 431-451; 432-452; 433-455; 434-452; 504-526; and 506-526 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

~~3. The dsRNA agent of claim 1 or 2, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-959917.1; AD-959918.1; AD-960096.1; AD-960064.1; AD-959914.1; AD-959941.1; AD-960031.1; AD-960063.1; AD-960293.1; AD-960288.1; AD-960445.1; AD-960292.1; AD-960475.1; AD-960442.1; AD-~~

960470.1; AD-960436.1; AD-960446.1; AD-960474.1; AD-960294.1; AD-960471.1; AD-960314.1; AD-960443.1; AD-960282.1; AD-960283.1; AD-80794.7; AD-960478.1; AD-960481.1; and AD-960482.1.

4. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 235-257; 238-260; 242-264; 243-265; 244-266; 426-448; 430-450; 431-453; 432-454; 433-455; 435-457; 436-458; 499-521; 503-525; and 504-526 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

5. The dsRNA agent of claim 1 or 2, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by not more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-959917.1; AD-960064.1; AD-960031.1; AD-960063.1; AD-960293.1; AD-960288.1; AD-960445.1; AD-960292.1; AD-960475.1; AD-960442.1; AD-960470.1; AD-960436.1; AD-960446.1; AD-960474.1; AD-960294.1; AD-960443.1; AD-80794.7; and AD-959910.1.

6. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 232-254; 239-261; 242-264; 244-266; 258-280; 264-286; 268-290, 429-451; 430-450; 430-452; 433-455; 434-456; 435-457; 500-522; 503-525; 507-529; and 510-532 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

7. The dsRNA agent of claim 1 or 2, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by not more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-80794.8; AD-959907.2; AD-959914.2; AD-959916.2; AD-959932.2; AD-960314.2; AD-959941.2; AD-960030.2; AD-960062.2; AD-960064.2; AD-960065.2; AD-960066.2; AD-960294.2; AD-960471.2; AD-960474.2; AD-960478.2; and AD-960481.2.

~~8. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 (APOC3) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 429-451; 430-452; 431-451; 432-452; 433-455; 504-526; and 506-526 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.~~

~~9. The dsRNA agent of claim 1 or 2, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by not more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of 960064.2; AD-960065.2; AD-960066.2; AD-960294.2; AD-960471.2; AD-960474.2; AD-960478.2; and AD-960481.2.~~

~~10. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 429-455 or 504-532 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.~~

~~11. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 429-451; 430-452; 431-451; 432-452; 433-455; 434-452; 504-526; and 506-526 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.~~

~~12. The dsRNA agent of claim 10 or 11, wherein the sense strand comprises at least 15 contiguous nucleotides differing by not more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of nucleotides 434-452 of SEQ ID NO:1.~~

~~13. The dsRNA agent of any one of claims 10-12, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by not more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-960030;~~

~~AD-960064; AD-1143243; AD-1143245; AD-1143247; AD-1143249; AD-1143256; AD-1143260; AD-1143278; AD-1143287; AD-1143295; AD-1143299; AD-1143302; and AD-1143305.~~

~~14. The dsRNA agent of any one of claims 10-13, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by not more than 0, 1, 2, or 3 nucleotides from the antisense strand nucleotide sequence of duplex AD-1143243.~~

~~15. The dsRNA agent of any one of claims 10-13, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by not more than 0, 1, 2, or 3 nucleotides from the antisense strand nucleotide sequence of duplex AD-1143278 or AD-960064.~~

26~~16~~. The dsRNA agent of any one of claims 24~~1-15~~ and 25, wherein the dsRNA agent comprises at least one modified nucleotide.

27~~17~~. The dsRNA agent of any one of claims 24~~1~~-26~~16~~, wherein substantially all of the nucleotides of the sense strand; substantially all of the nucleotides of the antisense strand comprise a modification; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

28~~18~~. The dsRNA agent of any one of claims 24~~1~~-27~~17~~, wherein all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

29~~19~~. The dsRNA agent ~~of any one~~ of claims 26~~16~~-28~~18~~, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

~~20. The dsRNA agent of any one of claims 16-18, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C-allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.~~

~~21. The dsRNA agent of any one of claims 16-18, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and, a vinyl-phosphonate nucleotide; and combinations thereof.~~

~~22. The dsRNA agent of any one of claims 16-18, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, and a 2'-fluoro modified nucleotide; and combinations thereof.~~

~~23. The dsRNA agent of any one of claims 16-18, wherein at least one of the modifications on the nucleotides is a thermally-destabilizing nucleotide modification.~~

~~24. The dsRNA agent of claim 23, wherein the thermally-destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA).~~

30~~25~~. The dsRNA agent of any one of claims 1- and 24-29, wherein the double stranded region is 19-30 nucleotide pairs in length.

~~26. The dsRNA agent of claim 25, wherein the double stranded region is 19-25 nucleotide pairs in length.~~

~~27. The dsRNA agent of claim 25, wherein the double stranded region is 19-23 nucleotide pairs in length.~~

~~28. The dsRNA agent of claim 25, wherein the double stranded region is 23-27 nucleotide pairs in length.~~

~~29. The dsRNA agent of claim 25, wherein the double stranded region is 21-23 nucleotide pairs in length.~~

3130. The dsRNA agent of any one of claims 1- and 24-309, wherein each strand is independently no more than 30 nucleotides in length.

~~31. The dsRNA agent of any one of claims 1-30, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.~~

~~32. The dsRNA agent of any one of claims 1-31, wherein the region of complementarity is at least 17 nucleotides in length.~~

~~33. The dsRNA agent of any one of claims 1-32, wherein the region of complementarity is between 19 and 23 nucleotides in length.~~

~~34. The dsRNA agent of any one of claims 1-31, wherein the region of complementarity is 19 nucleotides in length.~~

3235. The dsRNA agent of any one of claims 1- and 24-3134, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

~~36. The dsRNA agent of any one of claims 1-34, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.~~

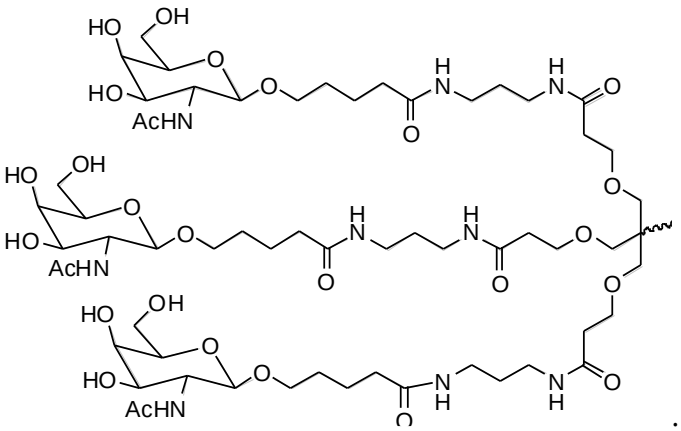
3337. The dsRNA agent of any one of claims 241-3236, further comprising a ligand.

3438. The dsRNA agent of claim 3337, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

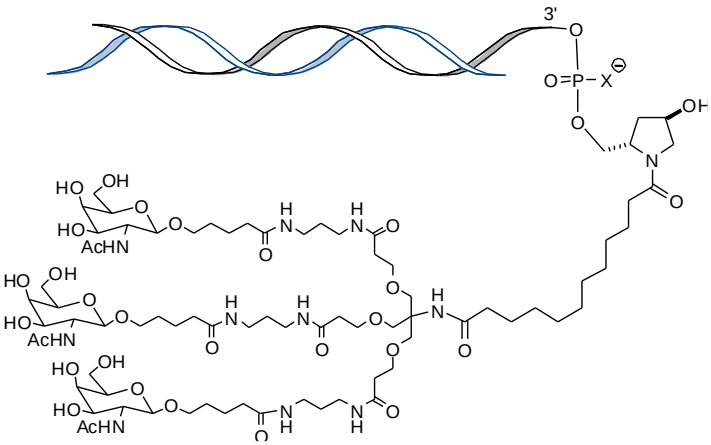
3539. The dsRNA agent of claim 337 or 348, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

3640. The dsRNA agent of any one of claims 337-359, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

3741. The dsRNA agent of any one of claims 337-3640, wherein the ligand is



3842. The dsRNA agent of claim 3741, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

3943. The dsRNA agent of claim 3842, wherein the X is O.

4044. The dsRNA agent of any one of claims 241-3943, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

~~45. The dsRNA agent of claim 44, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3' terminus of one strand.~~

~~46. The dsRNA agent of claim 45, wherein the strand is the antisense strand.~~

~~47. The dsRNA agent of claim 45, wherein the strand is the sense strand.~~

~~48. The dsRNA agent of claim 44, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5' terminus of one strand.~~

49. The dsRNA agent of claim 48, wherein the strand is the antisense strand.

50. The dsRNA agent of claim 48, wherein the strand is the sense strand.

51. The dsRNA agent of claim 44, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

52. The dsRNA agent of claim 51, wherein the strand is the antisense strand.

53. The dsRNA agent of any one of claims 1-52, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

54. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of CUUAAAAGGGACAGUAUUCUA (SEQ ID NO:13), and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of UAGAAUACUGUCCCUUUUAAGCC (SEQ ID NO:14),

wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification,

wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and

wherein at least one strand is conjugated to a ligand.

55. The dsRNA agent of claim 54, wherein the sense strand comprises 2-6 2'-fluoro modified nucleotides.

56. The dsRNA agent of claim 54 or 55, wherein the antisense strand comprises no more than 4 2'-fluoro modified nucleotides.

57. The dsRNA agent of any one of claims 54-56 wherein the antisense strand comprises 1-5 deoxy-modified nucleotides.

~~58. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,~~

~~wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,~~

~~wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of nucleotides 429-456 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2,~~

~~wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification, and a deoxy-modification,~~

~~wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and wherein at least one strand is conjugated to a ligand.~~

~~59. The dsRNA agent of claim 58, wherein the sense strand comprises 2-6 2'-fluoro modified nucleotides.~~

~~60. The dsRNA agent of claim 58 or 59, wherein the sense strand comprises 4 2'-fluoro modified nucleotides.~~

~~61. The dsRNA agent of any one of claims 58-60, wherein the antisense strand comprises 2-4 2'-fluoro modified nucleotides.~~

~~62. The dsRNA agent of claim 61, wherein the antisense strand comprises 2 2'-fluoro modified nucleotides.~~

~~63. The dsRNA agent of any one of claims 58-62, wherein the antisense strand comprises 1-5 2'-deoxy-modified nucleotides.~~

~~64. The dsRNA agent of claim 63, wherein the antisense strand comprises 3 2'-deoxy-modified nucleotides.~~

~~65. The dsRNA agent of any one of claims 58-64, wherein the sense strand comprises 4 2'-fluoro modified nucleotides at nucleotides 7 and 9-11, counting from the 5'-end, and the antisense strand comprises 2 2'-fluoro modified nucleotides at nucleotides 14 and 16, counting from the 5'-end, and 3 2'-deoxy-modified nucleotides at nucleotides 2, 5, and 7, counting from the 5'-end.~~

66. The dsRNA agent of any one of claims 58-65, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5’- terminus.

67. The dsRNA agent of any one of claims 58-66, wherein the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at both the 5’- and the 3’- terminus.

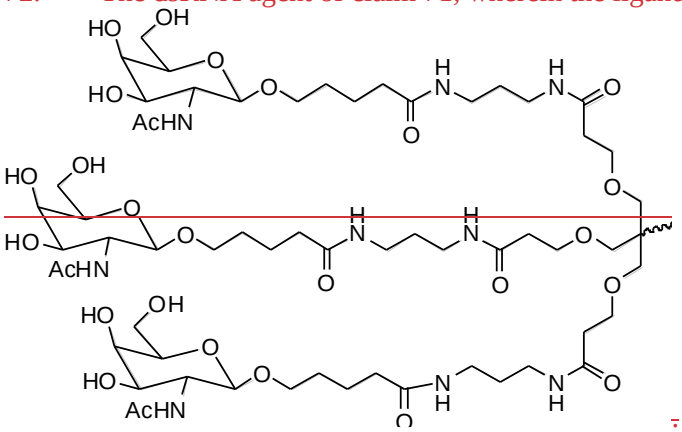
68. The dsRNA agent of any one of claims 58-67, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5’- terminus and the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at both the 5’- and the 3’- terminus.

69. The dsRNA agent of any one of claims 58-68, wherein the ligand is conjugated to the 3’- end of the sense strand.

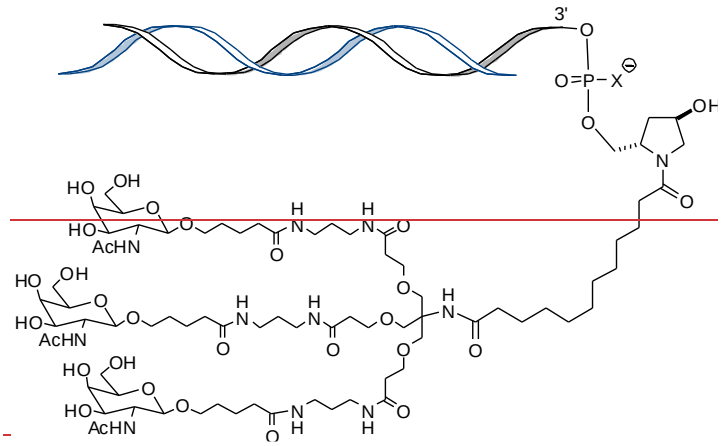
70. The dsRNA agent of any one of claims 58-69, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

71. The dsRNA agent of claim 70, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

72. The dsRNA agent of claim 71, wherein the ligand is



73. The dsRNA agent of claim 72, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O.

74. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

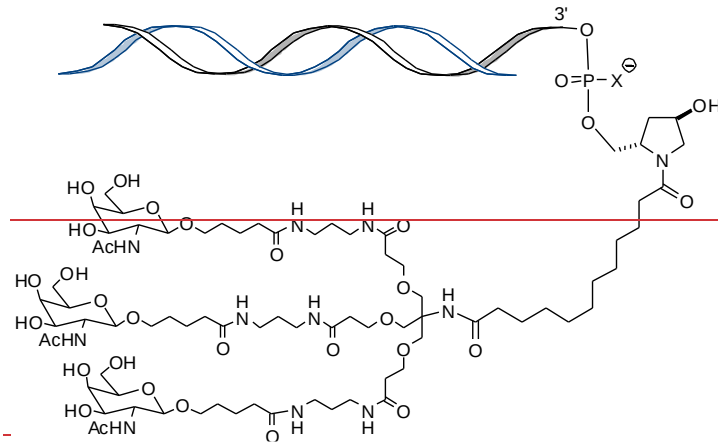
wherein the sense strand differs by no more than 3 modified nucleotides from the nucleotide sequence of 5’- csusuaaaAfgGfGfAfcaguauucua-3’ (SEQ ID NO:15) and wherein the antisense strand differs by no more than 3 modified nucleotides from the nucleotide sequence of 5’-usdAsgadAudAcuguccCfuUfuuaagscsc-3’ (SEQ ID NO:16),

wherein a, g, c and u are 2′-O-methyl (2′-OMe) A, G, C, and U respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U respectively; dA is a 2`-deoxyadenosine-3`-phosphate nucleotide; and s is a phosphorothioate linkage.

75. The dsRNA agent of claim 74, wherein the sense strand differs by no more than 2 modified nucleotides from the nucleotide sequence of 5’- csusuaaaAfgGfGfAfcaguauucua-3’ (SEQ ID NO:15) and wherein the antisense strand differs by no more than 2 modified nucleotides from the nucleotide sequence of 5’-usdAsgadAudAcuguccCfuUfuuaagscsc-3’ (SEQ ID NO:16).

76. The dsRNA agent of claim 74, wherein the sense strand differs by no more than 1 modified nucleotide from the nucleotide sequence of 5’- csusuaaaAfgGfGfAfcaguauucua-3’ (SEQ ID NO:15) and wherein the antisense strand differs by no more than 1 modified nucleotides from the nucleotide sequence of 5’-usdAsgadAudAcuguccCfuUfuuaagscsc-3’ (SEQ ID NO:16).

77. The dsRNA agent of claim 74, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O.

78. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence of 5'-csusuaaaAfgGfGfAfcaguauucua-3' (SEQ ID NO:15) and the antisense strand comprises the nucleotide sequence of 5'- usdAsgadAudAcuguccCfuUfuuaagscsc -3' (SEQ ID NO:16),

wherein a, g, c and u are 2′-O-methyl (2′-OMe) A, G, C, and U respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U respectively; dA is a 2`-deoxyadenosine-3`-phosphate nucleotide; and s is a phosphorothioate linkage.

79. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence of 5'-csusuaaaAfgGfGfAfcaguauucuaL96-3' (SEQ ID NO:17) and the antisense strand comprises the nucleotide sequence of 5'- usdAsgadAudAcuguccCfuUfuuaagscsc -3' (SEQ ID NO:16),

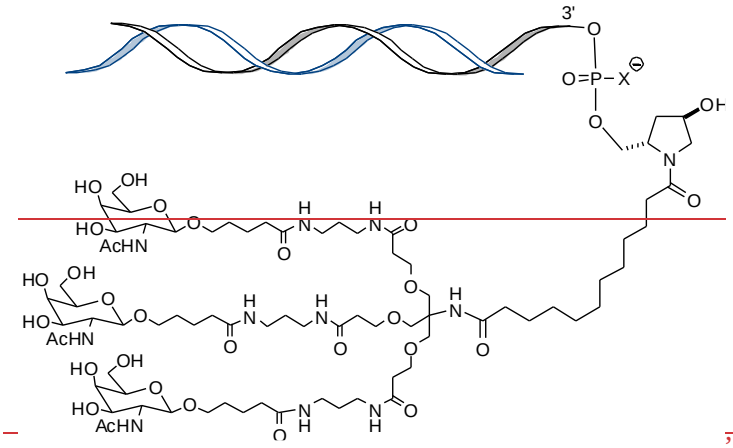
wherein a, g, c and u are 2′-O-methyl (2′-OMe) A, G, C, and U respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U respectively; dA is a 2`-deoxyadenosine-3`-phosphate nucleotide; s is a phosphorothioate linkage, and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

80. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence of 5'-csusuaaaAfgGfGfAfcaguauucua-3' (SEQ ID NO:15) and the antisense strand comprises the nucleotide sequence of 5'- usdAsgadAudAcuguccCfuUfuuaagscsc -3' (SEQ ID NO:16),

wherein a, g, c and u are 2′-O-methyl (2′-OMe) A, G, C, and U respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U respectively; dA is a 2`-deoxyadenosine-3`-phosphate nucleotide; and s is a phosphorothioate linkage; and wherein the 3'-end of the sense strand is conjugated to a ligand as shown in the following schematic:



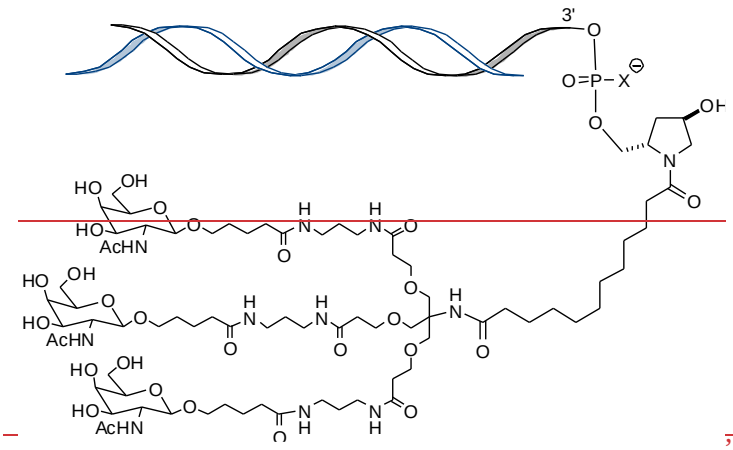
, wherein X is O.

81. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of apolipoprotein C3 in a cell,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand consists of the nucleotide sequence of 5'-csusuaaaAfgGfGfAfcaguauucua-3' (SEQ ID NO:15) and the antisense strand consists of the nucleotide sequence of 5'- usdAsgadAudAcuguccCfuUfuuaagscsc -3' (SEQ ID NO:16),

wherein a, g, c and u are 2′-O-methyl (2′-OMe) A, G, C, and U respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U respectively; dA is a 2`-deoxyadenosine-3`-phosphate nucleotide; and s is a phosphorothioate linkage; and wherein the 3'-end of the sense strand is conjugated to a ligand as shown in the following schematic:



, wherein X is O.

4182. A cell containing the dsRNA agent of any one of claims 1-4081.

4283. A pharmaceutical composition for inhibiting expression of a gene encoding apolipoprotein C3 (APOC3) comprising the dsRNA agent of any one of claims 1-4081.

4384. The pharmaceutical composition of claim 4283, wherein dsRNA agent is in an unbuffered solution.

4485. The pharmaceutical composition of claim 4384, wherein the unbuffered solution is saline or water.

4586. The pharmaceutical composition of claim 4283, wherein said dsRNA agent is in a buffer solution.

4687. The pharmaceutical composition of claim 4586, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

4788. The pharmaceutical composition of claim 4687, wherein the buffer solution is phosphate buffered saline (PBS).

4889. An *in vitro* method of inhibiting expression of an apolipoprotein C3 (APOC3) gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-4081, or the pharmaceutical composition of any one of claims 4283-4788, thereby inhibiting expression of the APOC3 gene in the cell.

~~90. The method of claim 89, wherein the cell is within a subject.~~

~~91. The method of claim 90, wherein the subject is a human.~~

~~92. The method of claim 91, wherein the subject has an apolipoprotein C3-associated disorder.~~

~~93. The method of claim 92, wherein the apolipoprotein C3-associated disorder is selected from the group consisting of hypertriglyceridemia, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, polycystic ovary syndrome, kidney disease, obesity, type 2 diabetes mellitus (insulin resistance), hypertension, artherosclerosis and pancreatitis.~~

4994. The method of ~~any one of~~ claim~~s~~ 4889-93, wherein contacting the cell with the dsRNA agent inhibits the expression of apolipoprotein C3 by at least 50%~~, 60%, 70%, 80%, 90%, or 95%~~.

5095. The method of ~~any one of~~ claim~~s~~ 48 or 4989-94, wherein inhibiting expression of apolipoprotein C3 decreases apolipoprotein C3 protein level in serum of the subject by at least 50%~~, 60%, 70%, 80%, 90%, or 95%~~.

5196. Use of the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 in the manufacture of a medicament for ~~A method of~~ treating a subject having a disorder that would benefit from reduction in apolipoprotein C3 expression~~, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-81, or the pharmaceutical composition of any one of claims 83-88, thereby treating the subject having the disorder that would benefit from reduction in apolipoprotein C3 expression~~.

~~97. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in apolipoprotein C3 expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-81, or the pharmaceutical composition of any one of claims 83-88, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in apolipoprotein C3 expression.~~

5298. The use~~method~~ of claim 5196 ~~or 97~~, wherein the disorder is an apolipoprotein C3-associated disorder.

5399. The use~~method~~ of claim 5298, wherein the apolipoprotein C3-associated disorder is selected from the group consisting of hypertriglyceridemia, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, polycystic ovary syndrome, kidney disease, obesity, type 2 diabetes mellitus (insulin resistance), hypertension, artherosclerosis and pancreatitis.

54~~100~~. The use~~method~~ of claim 5298, wherein the apolipoprotein C3-associated disorder is hypertriglyceridemia.

55~~101~~. The use~~method~~ of claim any one of claims 5196-54~~100~~, wherein the subject is human.

56~~102~~. The use~~method~~ of any one of claims 5196-55~~101~~, wherein ~~the administration of~~ the agent that is to be administered to the subject causes a decrease in hypertriglycedemia and/or a decrease in APOC3 protein accumulation.

57~~103~~. The use~~method~~ of any one of claims 5196-56~~102~~, wherein the dsRNA agent is to be administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

58104. The usemethod of any one of claims 5196-57103, wherein the dsRNA agent is to be administered to the subject subcutaneously.

~~105. The method of any one of claims 96-104, further comprising determining the level of apolipoprotein C3 in a sample(s) from the subject.~~

~~106. The method of claim 105, wherein the level of apolipoprotein C3 in the subject sample(s) is a apolipoprotein C3 protein level in a blood or serum sample(s).~~

59107. The usemethod of any one of claims 5196-58106, ~~further comprising administering to the~~ wherein ~~subject~~ an additional therapeutic agent for treatment of hemolysis is to be further administered to the subject.

60108. A kit comprising the dsRNA agent of any one of claims 1-4081 or the pharmaceutical composition of any one of claims 4283-4788.

61109. A vial comprising the dsRNA agent of any one of claims 1-4081 or the pharmaceutical composition of any one of claims 4283-4788.

62110. A syringe comprising the dsRNA agent of any one of claims 1-4081 or the pharmaceutical composition of any one of claims 4283-4788.

63. The dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 for use in therapy.