

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.

5 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
10 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
15 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.

20 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-
25 522; 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-
30 260; 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-
35 266; 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
5 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
10 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.

15 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
20 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
25 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.

30 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
35 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
5 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.

10 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,

5 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
10 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
15 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
20 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
25 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
30 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
35 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,

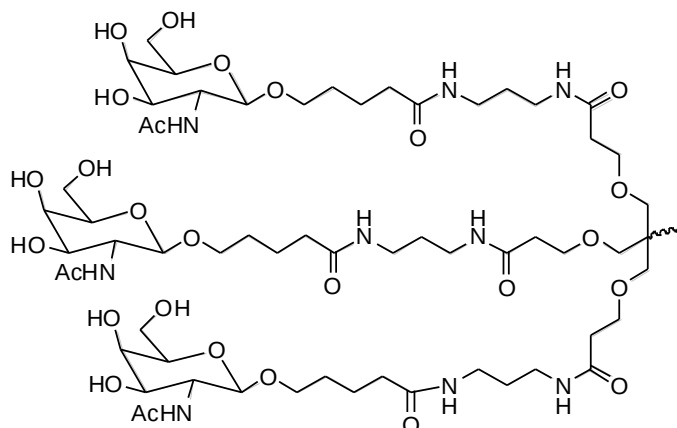
wherein both the sense strand and the antisense strand independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage, and wherein at least one strand is conjugated to a ligand.

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

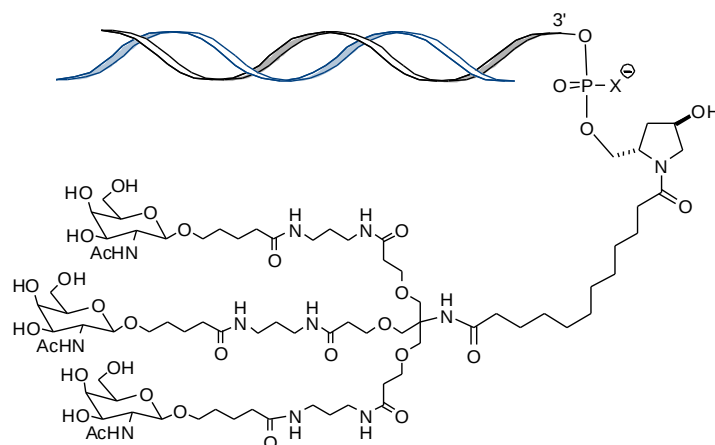
10. The dsRNA agent of any one of claims 4-9, wherein the sense strand comprises 4 2'-fluoro modified nucleotides.

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. 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. 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.

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

27. The dsRNA agent of any one of claims 24-26, 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. The dsRNA agent of any one of claims 24-27, 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. The dsRNA agent of claims 26-28, 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.

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

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

32. The dsRNA agent of any one of claims 1 and 24-31, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

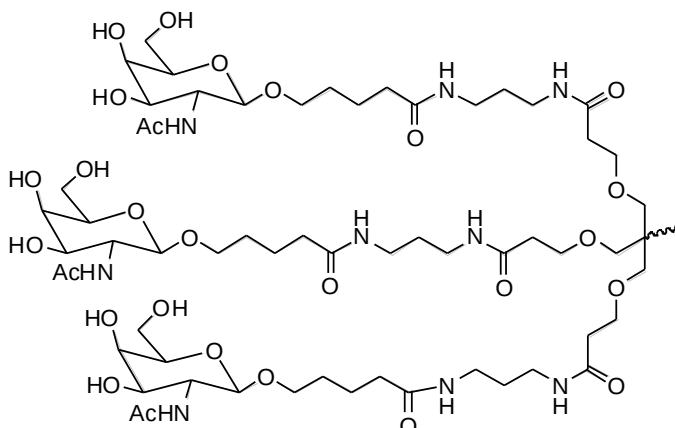
33. The dsRNA agent of any one of claims 24-32, further comprising a ligand.

34. The dsRNA agent of claim 33, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

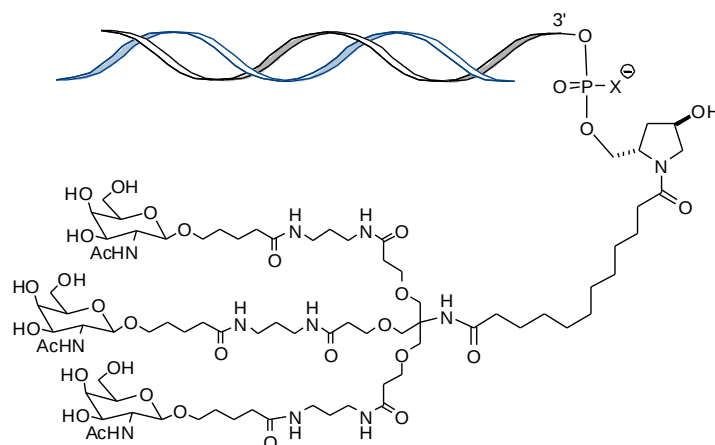
35. The dsRNA agent of claim 33 or 34, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

36. The dsRNA agent of any one of claims 33-35, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

37. The dsRNA agent of any one of claims 33-36, wherein the ligand is



38. The dsRNA agent of claim 37, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

39. The dsRNA agent of claim 38, wherein the X is O.

40. The dsRNA agent of any one of claims 24-39, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

41. A cell containing the dsRNA agent of any one of claims 1-40.

42. A pharmaceutical composition for inhibiting expression of a gene encoding apolipoprotein C3 (APOC3) comprising the dsRNA agent of any one of claims 1-40.
- 5 43. The pharmaceutical composition of claim 42, wherein dsRNA agent is in an unbuffered solution.
44. The pharmaceutical composition of claim 43, wherein the unbuffered solution is saline or water.
- 10 45. The pharmaceutical composition of claim 42, wherein said dsRNA agent is in a buffer solution.
46. The pharmaceutical composition of claim 45, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.
- 15 47. The pharmaceutical composition of claim 46, wherein the buffer solution is phosphate buffered saline (PBS).
48. An *in vitro* method of inhibiting expression of an apolipoprotein C3 (APOC3) gene in a cell, 20 the method comprising contacting the cell with the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47, thereby inhibiting expression of the APOC3 gene in the cell.
49. The method of claim 48, wherein contacting the cell with the dsRNA agent inhibits the 25 expression of apolipoprotein C3 by at least 50%.
50. The method of claim 48 or 49, wherein inhibiting expression of apolipoprotein C3 decreases apolipoprotein C3 protein level in serum of the subject by at least 50%.
- 30 51. 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 treating a subject having a disorder that would benefit from reduction in apolipoprotein C3 expression.
52. The use of claim 51, wherein the disorder is an apolipoprotein C3-associated disorder. 35
53. The use of claim 52, 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, arteriosclerosis and pancreatitis.

54. The use of claim 52, wherein the apolipoprotein C3-associated disorder is
5 hypertriglyceridemia.

55. The use of claim any one of claims 51-54, wherein the subject is human.

56. The use of any one of claims 51-55, wherein the agent that is to be administered to the
10 subject causes a decrease in hypertriglyceridemia and/or a decrease in APOC3 protein accumulation.

57. The use of any one of claims 51-56, 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.

15 58. The use of any one of claims 51-57, wherein the dsRNA agent is to be administered to the
subject subcutaneously.

59. The use of any one of claims 51-58, wherein an additional therapeutic agent for treatment of
hemolysis is to be further administered to the subject.

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60. A kit comprising the dsRNA agent of any one of claims 1-40 or the pharmaceutical
composition of any one of claims 42-47.

61. A vial comprising the dsRNA agent of any one of claims 1-40 or the pharmaceutical
25 composition of any one of claims 42-47.

62. A syringe comprising the dsRNA agent of any one of claims 1-40 or the pharmaceutical
composition of any one of claims 42-47.

30 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.