

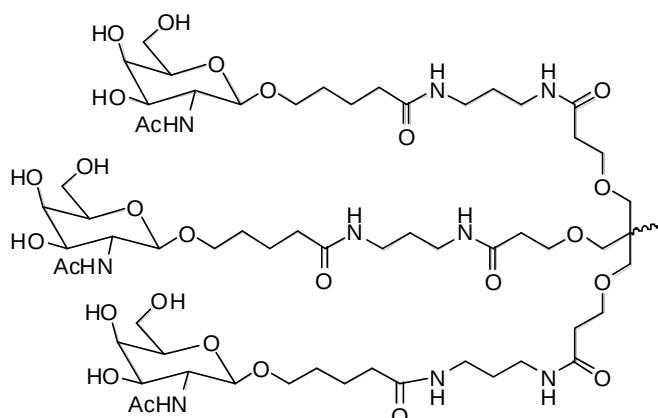
We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof,
5 wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 19 contiguous nucleotides of the nucleotide sequence 5'- AAGCUCCUUCUUUUUAUUGUU-3' of SEQ ID NO:46 and the antisense strand comprises at least 21 contiguous nucleotides of the nucleotide sequence of 5'-
10 AACAAUAAAAAGAAGGAGCUUGG -3' of SEQ ID NO:661,
wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification, and
wherein at least one of the modifications is a 2'-deoxy-nucleotide modification.
- 15 2. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1, wherein the double stranded region is 19-30 nucleotide pairs in length.
3. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1 or 2, wherein the double stranded region is 21-23 nucleotide pairs in length.
- 20 4. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-3, wherein each strand is independently 19-30 nucleotides in length.
5. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-4,
25 wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
6. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-5, further comprising a ligand.
- 30 7. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 6, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.
8. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 6 or 7, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

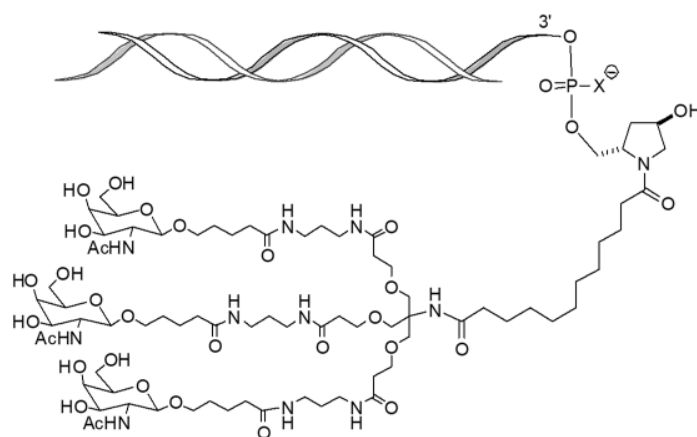
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9. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 6-8, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

5 10. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 9, wherein the ligand is



11. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 10, wherein the
10 dsRNA agent, or a pharmaceutically acceptable salt thereof, is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

15 12. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 11, wherein X is O.

13. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-12, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

14. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 13, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand; the 5'-terminus of one strand; or at both the 5'- and 3'-terminus of one strand.

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15. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-14, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

10 16. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-15, wherein the sense strand comprises the nucleotide sequence 5'- AAGCUCCUUCUUUUUAUUGUU-3' of SEQ ID NO:46.

15 17. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-16, wherein the sense strand comprises the nucleotide sequence 5'- AAGCUCCUUCUUUUUAUUGUU-3' of SEQ ID NO:46 and the antisense strand comprises the nucleotide sequence 5'- AACAAUAAAAAGAAGGAGCUUGG -3' of SEQ ID NO:661.

20 18. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-17, wherein the sense strand consists of the nucleotide sequence 5'- AAGCUCCUUCUUUUUAUUGUU-3' of SEQ ID NO:46 and the antisense strand consists of the nucleotide sequence 5'- AACAAUAAAAAGAAGGAGCUUGG -3' of SEQ ID NO:661.

25 19. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, wherein the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the antisense strand comprises the nucleotide sequence 5'- asdAscadAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

30 wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

35 20. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-19, wherein the sense strand consists of the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the antisense strand consists of the nucleotide sequence 5'- asdAscadAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

21. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-asdAscadAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

22. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 21, wherein the nucleotide sequence of the sense strand differs by no more than 3 bases from the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand differs by no more than 3 bases from the nucleotide sequence 5'-asdAscadAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

23. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 21 or 22, wherein the nucleotide sequence of the sense strand differs by no more than 2 bases from the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand differs by no more than 2 bases from the nucleotide sequence 5'-asdAscadAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

24. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 21-23, wherein the nucleotide sequence of the sense strand differs by no more than 1 base from the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide

sequence of the antisense strand differs by no more than 1 base from the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

25. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 21-24, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

26. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

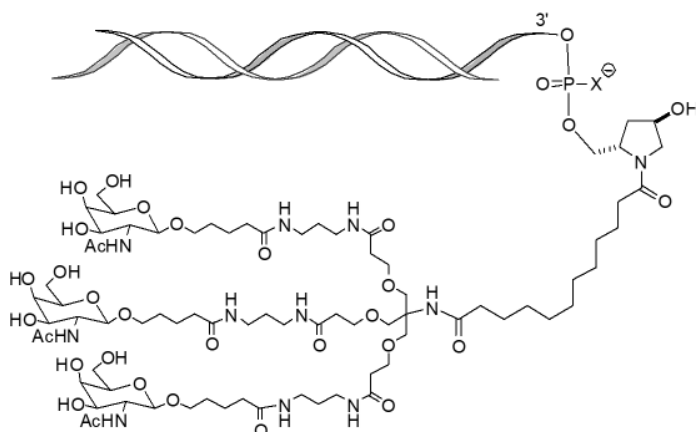
27. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 26, further comprising a ligand.

28. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage, and

wherein a ligand is conjugated to the 3'-end of the sense strand as shown in the following schematic



, wherein X is O.

29. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 28, which is in a salt form.

30. A pharmaceutical composition for inhibiting expression of a gene encoding ANGPTL3 comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-29.

31. The pharmaceutical composition of claim 30, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is present in an unbuffered solution.

32. The pharmaceutical composition of claim 31, wherein the unbuffered solution is saline or water.

33. The pharmaceutical composition of claim 30, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is present in a buffer solution.

34. The pharmaceutical composition of claim 33, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

35. The pharmaceutical composition of claim 33, wherein the buffer solution comprises phosphate buffered saline (PBS).

36. An *in vitro* method of inhibiting expression of an Angiopoietin-like 3 (ANGPTL3) gene in a cell, comprising contacting the cell with any of the dsRNA agent, or a pharmaceutically acceptable

salt thereof, of any one of claims 1-29 or the pharmaceutical composition of any one of claims 30-35, thereby inhibiting expression of the ANGPTL3 gene in the cell.

37. The method of claim 36, wherein, ANGPTL3 expression is inhibited by at least about 30%.

38. Use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-29 or the pharmaceutical composition of any one of claims 30-35 in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in Angiopoietin-like 3 (ANGPTL3) expression.

39. The use of claim 38, wherein the subject is a human.

40. The use of claim 38 or 39, wherein the disorder is an ANGPTL3-associated disorder.

41. The use of claim 40, wherein the ANGPTL3-associated disorder is a disorder of lipid metabolism.

42. The use of claim 41, wherein the disorder of lipid metabolism is hyperlipidemia or hypertriglyceridemia.

43. The use of any one of claims 38-42, wherein the medicament is to be subcutaneously administered.

44. Use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-29 or the pharmaceutical composition of any one of claims 30-35 in the manufacture of a first medicament and use of an additional therapeutic agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treatment of an ANGPTL3-associated disorder.

45. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-29 or the pharmaceutical composition of any one of claims 30-35 for use in therapy.

46. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-29 or the pharmaceutical composition of any one of claims 30-35, and an additional therapeutic agent for use in therapy.