

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

10 comprises at least 21 contiguous nucleotides of the nucleotide sequence of 5'- 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

15 wherein at least one of the modifications is a 2'-deoxy-nucleotide modification~~wherein the antisense strand comprises a region of complementarity to an mRNA encoding ANGPTL3, 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 2-3 and 7-8.~~

20 ~~2. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) 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 any one of the nucleotide sequence of nucleotides 58-80, 73-102, 73-124, 80-114, 291-320, 291-342, 307-336, 540-567, 540-589 and 545-577 of SEQ ID NO: 1, and the antisense strand comprises at least 15~~

25 ~~contiguous nucleotides differing by no more than 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.~~

30 ~~3. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) 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 any one of the nucleotide sequence of nucleotides 58-80, 80-102; 84-106; 87-109; 91-113; 92-114; 186-208; 307-329; 308-330; 310-332; 314-336; 545-567; 551-573; 553-575; 554-576; 555-577; 1133-1155; or 1140-1162 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous~~

35 ~~nucleotides differing by no more than 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.~~

~~4. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) 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 any one of the nucleotide sequence of nucleotides 58-80, 91-113, or 92-114 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

5. ——— A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) 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 the nucleotide sequence of nucleotides 58-80 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

6. ——— The dsRNA agent of any one of claims 1-5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1331203.1; AD-1331206.1; AD-1331209.1; AD-1331212.1; AD-1331213.1; AD-1331329.1; AD-1331237.1; AD-1331238.1; AD-1331240.1; AD-1331244.1; AD-1331256.1; AD-1331262.1; AD-1331264.1; AD-1331265.1; AD-1331266.1; AD-1331316.1; AD-1331338.1; and AD-1479372.

7. ——— The dsRNA agent of any one of claims 1-5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1331203.1; AD-1331206.1; AD-1331209.1; AD-1331212.1; AD-1331213.1; AD-1331329.1; AD-1331240.1; AD-1331262.1; AD-1331264.1; AD-1331265.1 AD-1331266.1; and AD-1479372.

8. ——— The dsRNA agent of any one of claims 1-5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1331203.1; AD-1331206.1; AD-1331209.1; AD-1331212.1; AD-1331213.1; and AD-1479372.

9. ——— The dsRNA agent of any one of claims 1-5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1331212.1; AD-1331213.1; and AD-1479372.

10. — The dsRNA agent of any one of claims 1-5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from the antisense strand nucleotide sequence of AD-1479372.

11. — The dsRNA agent of any one of claims 1-10, wherein the dsRNA agent comprises at least one modified nucleotide.

12. — The dsRNA agent of any one of claims 1-11, 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.

13. — The dsRNA agent of any one of claims 1-12, 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.

14. — The dsRNA agent of any one of claims 11-13, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (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'-hydroxyl 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), a nucleotide comprising a 2' phosphate, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

15. — The dsRNA agent of any one of claims 11-13, 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.

16. — The dsRNA agent of any one of claims 11-13, 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), a nucleotide comprising a 2' phosphate, and, a vinyl-phosphonate nucleotide; and combinations thereof.

~~17. The dsRNA agent of any one of claims 11-13, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.~~

~~18. The dsRNA agent of claim 17, 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).~~

~~219. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-18, wherein the double stranded region is 19-30 nucleotide pairs in length.~~

~~20. The dsRNA agent of claim 19, wherein the double stranded region is 19-25 nucleotide pairs in length.~~

~~21. The dsRNA agent of claim 19, wherein the double stranded region is 19-23 nucleotide pairs in length.~~

~~22. The dsRNA agent of claim 19, wherein the double stranded region is 23-27 nucleotide pairs in length.~~

~~323. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1 or 29, wherein the double stranded region is 21-23 nucleotide pairs in length.~~

~~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.~~

~~24. The dsRNA agent of any one of claims 1-23, wherein each strand is independently no more than 30 nucleotides in length.~~

~~25. The dsRNA agent of any one of claims 1-24, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.~~

~~26. The dsRNA agent of any one of claims 1-25, wherein the region of complementarity is at least 17 nucleotides in length.~~

~~27. The dsRNA agent of any one of claims 1-26, wherein the region of complementarity is between 19 and 23 nucleotides in length.~~

~~28. The dsRNA agent of any one of claims 1-27, wherein the region of complementarity is 19 nucleotides in length.~~

~~529.~~ The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-
5 ~~428~~, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

~~30. The dsRNA agent of any one of claims 1-28, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.~~

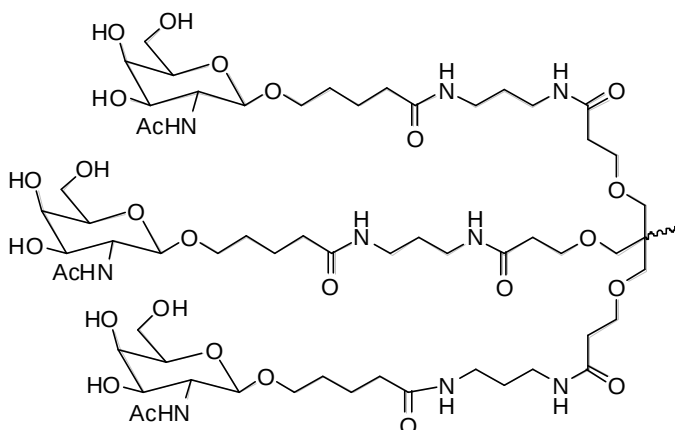
10 631. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-
530, further comprising a ligand.

732. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 631, wherein
the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

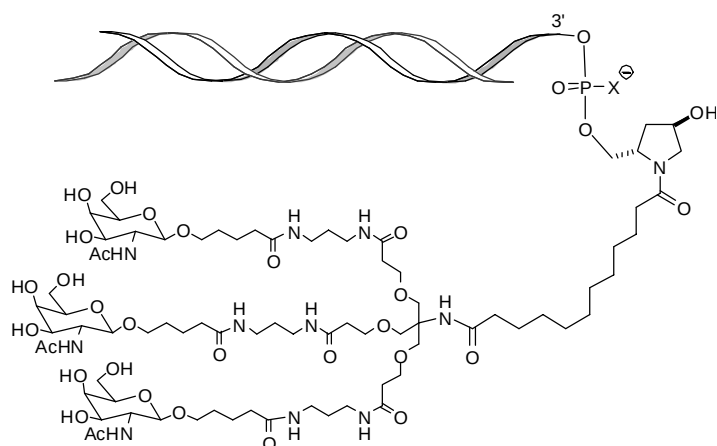
15 338. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 631 or 732,
wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

934. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims
20 631-833, wherein the ligand is one or more GalNAc derivatives attached through a monovalent,
bivalent, or trivalent branched linker.

1035. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 933 or 34,
wherein the ligand is



1136. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1035, wherein
the dsRNA agent, or a pharmaceutically acceptable salt thereof, is conjugated to the ligand as
shown in the following schematic



~~3712.~~ The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim ~~1136~~, wherein ~~the~~-X is O.

~~1338~~. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-
~~1237~~, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, further
comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

1439. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1338, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand;

~~40. The dsRNA agent of claim 39, wherein the strand is the antisense strand.~~

~~41. The dsRNA agent of claim 39, wherein the strand is the sense strand.~~

42. — The dsRNA agent of claim 38, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand; or:

~~43. The dsRNA agent of claim 42, wherein the strand is the antisense strand.~~

~~44. The dsRNA agent of claim 42, wherein the strand is the sense strand.~~

45.— The dsRNA agent of claim 38, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at both the 5'- and 3'-terminus of one strand.

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.

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.

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'-AACAAUAAAAGAAGGAGCUUGG-3' of SEQ ID NO:661.

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'-AACAAUAAAAGAAGGAGCUUGG-3' of SEQ ID NO:661.

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,

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.

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.

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

~~47. The dsRNA agent of any one of claims 1-46, wherein the base pair at the 1 position of the 5' end of the antisense strand of the duplex is an AU base pair.~~

~~48. The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' (SEQ ID NO: 18) and the nucleotide sequence of the~~

antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-

asdAscAdAudAaaaadGaAfggagcuusgsg-3' (SEQ ID NO: 19),

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

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49. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 3 bases from the nucleotide sequence 5'-

asasgcuccuUfCfUfuuuuuauuguu-3' (SEQ ID NO: 18) and the nucleotide sequence of the

antisense strand differs by no more than 3 bases from the nucleotide sequence 5'-

10 asdAscAdAudAaaaadGaAfggagcuusgsg-3' (SEQ ID NO: 19),

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

50. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 2 bases from the nucleotide sequence 5'-

asasgcuccuUfCfUfuuuuuauuguu-3' (SEQ ID NO: 18) and the nucleotide sequence of the

antisense strand differs by no more than 2 bases from the nucleotide sequence 5'-

15 asdAscAdAudAaaaadGaAfggagcuusgsg-3' (SEQ ID NO: 19),

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

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51. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 1 base from the nucleotide sequence 5'-

asasgcuccuUfCfUfuuuuuauuguu-3' (SEQ ID NO: 18) and the nucleotide sequence of the

antisense strand differs by no more than 1 base from the nucleotide sequence 5'-

25 asdAscAdAudAaaaadGaAfggagcuusgsg-3' (SEQ ID NO: 19),

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

52. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuuauuguu-3' (SEQ ID

NO: 18) and the nucleotide sequence of the antisense strand comprises the nucleotide

sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' (SEQ ID NO: 19),

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

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53. — The dsRNA agent of any one of claims 48-52, further comprising a ligand.

2554. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims

21-2453, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

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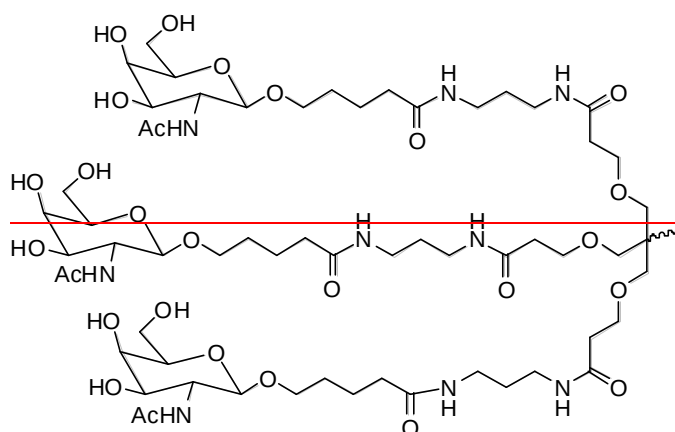
26. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-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.

55. The dsRNA agent of claim 53 or 54, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

56. The dsRNA agent of any one of claims 53-55, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

57. The dsRNA agent of any one of claims 53-56, wherein the ligand is

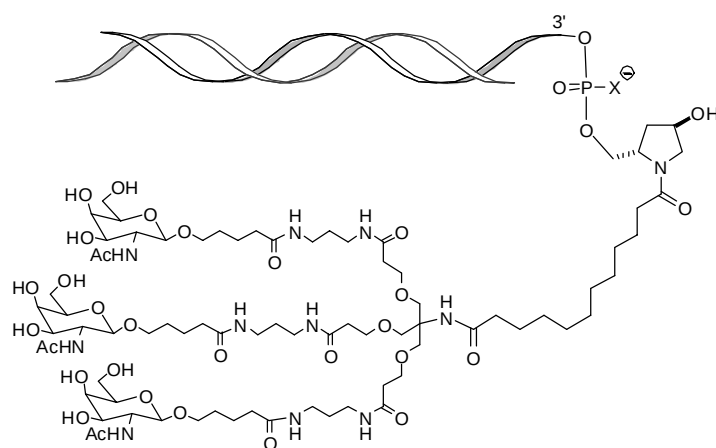


58. The dsRNA agent of any one of claims 48-57, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguuL96-3' (SEQ ID NO: 20) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' (SEQ ID NO: 19), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; dA and dG, are 2'-deoxy A and G; Cf and Uf are 2'-deoxy 2'-fluoro (2'-F) C and U; s is a phosphorothioate linkage, and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl]-4-hydroxyprolinol.

~~2859. The double stranded ribonucleic acid (dsRNA) agent of any one of claims 47-58 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 5'-asasgcuccuUfCfUfuuuuuauuguu-3' (SEQ ID NO: 18) 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 2'-deoxy-2'-fluoro (2'-F) C and U; 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.~~

~~60. The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'-asasgeucCfuUfCfUfuuuuuauuguu-3' (SEQ ID NO: 21) and the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-asAfscaaUfaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22); or~~

~~wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'-asgscuccUfuCfUfUfuuuuuauuguuu-3' (SEQ ID NO: 23) and the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-asAfsacaAfuaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24);~~

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

~~61. The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 3 bases from the nucleotide sequence 5'-~~

asasgcucCfuUfCfUfuuuuauuguu-3' (SEQ ID NO: 21) and the nucleotide sequence of the antisense strand differs by no more than 3 bases from the nucleotide sequence 5'-asAfscaaUfaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22); or

wherein the nucleotide sequence of the sense strand differs by no more than 3 bases from the nucleotide sequence 5'-asgscuccUfuCfUfufuuuauuguuu-3' (SEQ ID NO: 23) and the nucleotide sequence of the antisense strand differs by no more than 3 bases from the nucleotide sequence 5'-asAfsacaAfuaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24);

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

62. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 2 bases from the nucleotide sequence 5'-asasgcucCfuUfCfUfuuuuauuguu-3' (SEQ ID NO: 21) and the nucleotide sequence of the antisense strand differs by no more than 2 bases from the nucleotide sequence 5'-asAfscaaUfaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22); or

wherein the nucleotide sequence of the sense strand differs by no more than 2 bases from the nucleotide sequence 5'-asgscuccUfuCfUfufuuuauuguuu-3' (SEQ ID NO: 23) and the nucleotide sequence of the antisense strand differs by no more than 2 bases from the nucleotide sequence 5'-asAfsacaAfuaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24);

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

63. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand differs by no more than 1 base from the nucleotide sequence 5'-asasgcucCfuUfCfUfuuuuauuguu-3' (SEQ ID NO: 21) and the nucleotide sequence of the antisense strand differs by no more than 1 base from the nucleotide sequence 5'-asAfscaaUfaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22); or

wherein the nucleotide sequence of the sense strand differs by no more than 1 base from the nucleotide sequence 5'-asgscuccUfuCfUfufuuuauuguuu-3' (SEQ ID NO: 23) and the nucleotide sequence of the antisense strand differs by no more than 1 base from the nucleotide sequence 5'-asAfsacaAfuaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24);

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

64. — The dsRNA agent of any one of claims 1-47, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcucCfuUfCfUfuuuuauuguu-3' (SEQ ID NO: 21) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asAfscaaUfaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22); or

wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asgscuccUfuCfUfufuuuauuguuu-3' (SEQ ID NO: 23) and the nucleotide sequence

of the antisense strand comprises the nucleotide sequence 5'-
asAfsacaAfuaaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24),
wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Cf and Uf are 2'-deoxy-
2'-fluoro (2'-F) C and U; s is a phosphorothioate linkage.

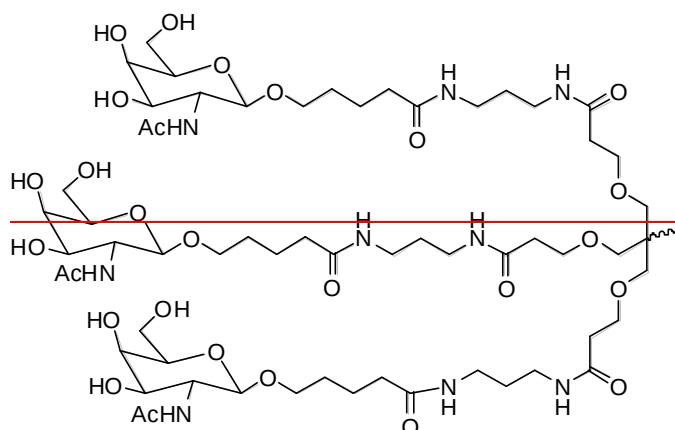
65. The dsRNA agent of any one of claims 60-64, further comprising a ligand.

66. The dsRNA agent of claim 65, wherein the ligand is conjugated to the 3' end of the
sense strand of the dsRNA agent.

67. The dsRNA agent of claim 65 or 66, wherein the ligand is an N-acetylgalactosamine
(GalNAc) derivative.

68. The dsRNA agent of any one of claims 65-67, wherein the ligand is one or more GalNAc
derivatives attached through a monovalent, bivalent, or trivalent branched linker.

69. The dsRNA agent of any one of claims 65-68, wherein the ligand is



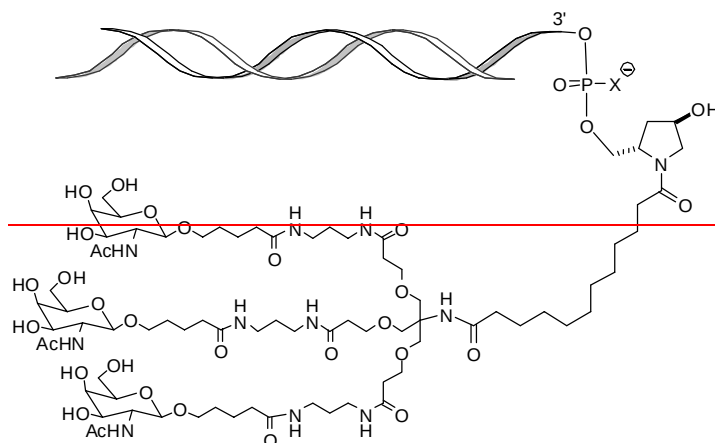
70. The dsRNA agent of any one of claims 60-69, wherein the nucleotide sequence of the
sense strand comprises the nucleotide sequence 5'-asasgcucCfuUfCfUfuuuuuauuguuL96-3'
(SEQ ID NO: 25) and the nucleotide sequence of the antisense strand comprises the nucleotide
sequence 5'-asAfscaaUfaaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22); or

wherein the nucleotide sequence of the sense strand comprises the nucleotide
sequence 5'-asgscuccUfuCfuUfUfuuuauuguuuL96-3' (SEQ ID NO: 281) and the nucleotide
sequence of the antisense strand comprises the nucleotide sequence 5'-
asAfsacaAfuaaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24)

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U; Cf and Uf are 2'-deoxy-
2'-fluoro (2'-F) C and U; s is a phosphorothioate linkage, and L96 is N-[tris(GalNAc-alkyl)-
amidodecanoyl]-4-hydroxyprolinol.

71. — The dsRNA agent of any one of claims 60-70, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asagcucCfuUfGfUfuuuuauuguu-3' (SEQ ID NO: 21) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asAfscaaUfaaaaagaAfgGfagcuusasa-3' (SEQ ID NO: 22);

wherein a, g, c and u are 2'-O methyl (2'-OMe) A, G, C, and U; Cf and Uf are 2'-deoxy-2'-fluoro (2'-F) C and U; 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

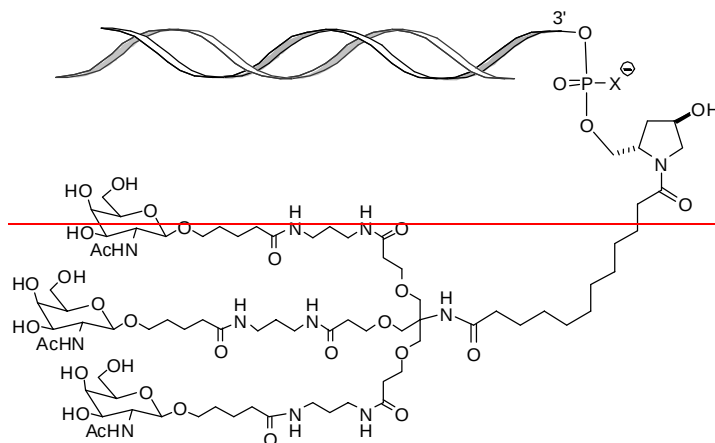


and,

wherein X is O.

72. — The dsRNA agent of any one of claims 60-70, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asgscuccUfuCfUfUfuuuuauuguuu-3' (SEQ ID NO: 23) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asAfsacaAfuaaaaagAfaGfgagcususa-3' (SEQ ID NO: 24)

wherein a, g, c and u are 2'-O methyl (2'-OMe) A, G, C, and U; Cf and Uf are 2'-deoxy-2'-fluoro (2'-F) C and U; 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



and,

wherein X is O.

~~73. A cell containing the dsRNA agent of any one of claims 1-72.~~

3074. A pharmaceutical composition for inhibiting expression of a gene encoding ~~Angiopoietin-like 3 (ANGPTL3)~~ comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof,
5 of any one of claims 1-2972.

3175. The pharmaceutical composition of claim 3074, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is present in an unbuffered solution.

3276. The pharmaceutical composition of claim 3175, wherein the unbuffered solution is saline or water.

3377. The pharmaceutical composition of claim 3074, wherein ~~thesaid~~ dsRNA agent, or a pharmaceutically acceptable salt thereof, is present in a buffer solution.

3478. The pharmaceutical composition of claim 3377, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

3579. The pharmaceutical composition of claim 3378, wherein the buffer solution ~~comprises~~ is phosphate buffered saline (PBS).

3680. An in-vitro method of inhibiting expression of an Angiopoietin-like 3 (ANGPTL3) gene in a cell, ~~the method~~ comprising contacting the cell with any of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-2972, or the pharmaceutical
25 composition of any one of claims 3074-3579, thereby inhibiting expression of the ANGPTL3 gene in the cell.

~~81. The method of claim 80, wherein the cell is within a subject.~~

~~82. The method of claim 81, wherein the subject is a human.~~

~~83. The method of claim 82, wherein the subject has an ANGPTL3-associated disorder.~~

~~84. The method of claim 83, wherein the ANGPTL3-associated disorder is a disorder of lipid metabolism.~~

~~85. The method of claim 84, wherein the disorder of lipid metabolism is hyperlipidemia or hypertriglyceridemia.~~

~~3786. The method of any one of claims 3680-85, wherein, contacting the cell with the dsRNA agent inhibits the expression of ANGPTL3 expression is inhibited by at least about 30%50%, 60%, 70%, 80%, 90%, or 95%.~~

~~87. The method of any one of claims 80-86, wherein inhibiting expression of ANGPTL3 decreases ANGPTL3 protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.~~

~~3888. Use of A method of treating a subject having a disorder that would benefit from reduction in Angiopoietin-like 3 (ANGPTL3) expression, comprising administering to the subject a therapeutically effective amount of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-2972, or the pharmaceutical composition of any one of claims 3074-3579, in the manufacture of a medicament for thereby treating a the subject having a the disorder that would benefit from reduction in Angiopoietin-like 3 (ANGPTL3) expression.~~

~~89. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in Angiopoietin-like 3 (ANGPTL3) expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-72, or the pharmaceutical composition of any one of claims 74-79, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in ANGPTL3 expression.~~

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

~~4090. The method use of claim 3888 or 3989, wherein the disorder is an ANGPTL3-associated disorder.~~

~~4191. The use method of claim 4090, wherein the ANGPTL3-associated disorder is a disorder of lipid metabolism.~~

~~4292. The use method of claim 4191, wherein the disorder of lipid metabolism is hyperlipidemia or hypertriglyceridemia.~~

~~93. The method of any one of claims 88-92, wherein the subject is a human.~~

~~94. The method of any one of claims 88-93, wherein the administration of the agent to the subject causes a decrease in one or more serum lipid and/or a decrease in ANGPTL3 protein accumulation.~~

~~95. The method of any one of claims 88-94, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.~~

4396. The usemethod of any one of claims 3888-4295, wherein the medicamentdsRNA-agent is to be subcutaneously administered to the subject subcutaneously.

97.—The method of any one of claims 88-96, further comprising determining the level of ANGPTL3 in a sample(s) from the subject.

98.—The method of claim 97, wherein the level of ANGPTL3 in the subject sample(s) is an ANGPTL3 protein level in a blood or serum sample(s).

4499. 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 The method of any one of claims 88-98, further comprising administering to the subject 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.

100.—A kit comprising the dsRNA agent of any one of claims 1-72 or the pharmaceutical composition of any one of claims 74-79.

101.—A vial comprising the dsRNA agent of any one of claims 1-72 or the pharmaceutical composition of any one of claims 74-79.

102.—A syringe comprising the dsRNA agent of any one of claims 1-72 or the pharmaceutical composition of any one of claims 74-79.

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.