We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid ~~dehydrogenases~~dehydrogenase type 13 (HSD17B13) in a cell, ~~wherein the dsRNA agent comprises~~comprising a sense strand and an antisense strand~~, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9.~~ forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides which differ by no more than three nucleotides from SEQ ID NO: 4498, and the antisense strand comprises a region of complementarity to at least 15 contiguous nucleotides differing by no more than three nucleotides from nucleotides 2242-2264 of SEQ ID NO: 1,

wherein at least one of the nucleotides of the sense strand and at least one of the nucleotides of the antisense strand comprises a modification selected from the group consisting of a 2′-O-methyl modification and a 2′-fluoro modification.

2. The dsRNA agent of claim 1, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified.

3. The dsRNA agent of claim 1, wherein the sense strand comprises no more than four 2′-fluoro modified nucleotides.

4. The dsRNA agent of claim 1, wherein the antisense strand comprises no more than six 2′-fluoro modified nucleotides.

5. The dsRNA agent of claim 1, wherein the antisense strand comprises at least one glycol-modified nucleotide.

6. The dsRNA agent of claim 5, wherein the antisense strand comprises a glycol modified nucleotide at position 7, counting from the 5′-end.

7. The dsRNA agent of claim 1, wherein the sense strand comprises four 2′-fluoro modified nucleotides at nucleotides 7 and 9-11, counting from the 5′-end, and

wherein the antisense strand comprises three 2′-fluoro modified nucleotides at nucleotides 2, 14, and 16, counting from the 5′-end, and one glycol modified nucleotide at nucleotide 7, counting from the 5′-end.

8. The dsRNA agent of claim 1, wherein: (a) the sense strand comprises at least one phosphorothioate or methylphosphonate internucleotide linkage; (b) the antisense strand comprises at least one phosphorothioate or methylphosphonate internucleotide linkage; or (c) both the sense strand and the antisense strand each comprise at least one phosphorothioate or methylphosphonate internucleotide linkage.

9. The dsRNA agent of claim 8, wherein the sense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at the 5′-terminus.

10. The dsRNA agent of claim 8, wherein the antisense strand comprises two phosphorothioate or methylphosphonate internucleotide linkages at each of the 5′-terminus and the 3′-terminus.

11. The dsRNA agent of claim 8, 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 each of the 5′-terminus and the 3′-terminus.

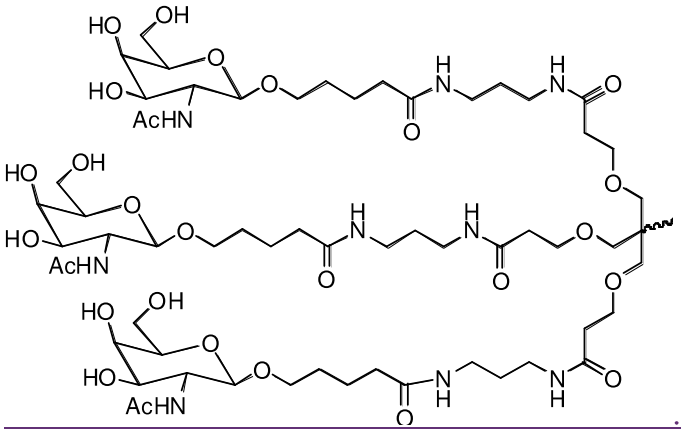
12. ~~2~~The dsRNA agent of claim 1, wherein at least one strand is conjugated to a ligand.

13. The dsRNA agent of claim 12, wherein the ligand is conjugated to the 3′-end of the sense strand.

14. The dsRNA agent of claim 1, wherein the ligand comprises an N-acetylgalactosamine (GalNAc) derivative.

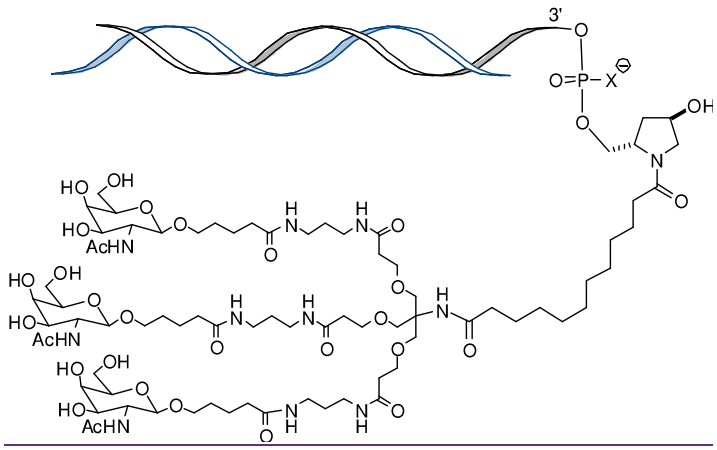
15. The dsRNA agent of claim 14, wherein the ligand comprises one or more GalNAc derivatives attached through a monovalent linker, a bivalent branched linker, or a trivalent branched linker.

16. The dsRNA agent of claim 15, wherein the ligand comprises:



.

17. The dsRNA agent of claim 16, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic:



and, wherein X is O.

18. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid ~~dehydrogenases~~dehydrogenase type 13 (HSD17B13) in a cell, ~~wherein said dsRNA agent comprises~~comprising a sense strand and an antisense strand ~~forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HSD17B13 which comprises at least 15 contiguous nucleotides differing by no~~

~~more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13.~~,

~~3. The dsRNA agent of claim 1 or 2,~~ wherein ~~said dsRNA agent comprises at least one modified nucleotide.~~

~~4. The dsRNA agent of any one of claims 1-3, wherein substantially all of the nucleotides of the sense strand comprise a modification.~~

~~5. The dsRNA agent of any one of claims 1-3, wherein substantially all of the nucleotides of the antisense strand comprise a modification.~~

~~6. The dsRNA agent of any one of claims 1-3, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.~~

~~7. A double stranded RNA (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein the double stranded RNA 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 the sense strand consists of the nucleotide sequence of SEQ ID NO:~~1 or 2~~ 4498 and the nucleotide sequence of the antisense strand ~~comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from~~consists of the nucleotide sequence of SEQ ID NO:~~8 or 9,~~ 4499, and

~~wherein substantially all~~at least one of the nucleotides of the sense strand and ~~substantially all~~at least one of ~~the~~ nucleotides of the antisense strand ~~are modified nucleotides,~~comprises a modification selected from the group consisting of a 2′-O-methyl modification and a 2′-fluoro modification.

~~wherein the sense strand is conjugated to a ligand attached at the 3’ terminus.~~

~~8~~19. The dsRNA agent of claim ~~7, wherein all of the nucleotides of the sense strand comprise a modification.~~

~~9. The dsRNA agent of claim 7, wherein all of the nucleotides of the antisense strand comprise a modification.~~

~~10. The dsRNA agent of claim 7~~18, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand ~~comprise a modification.~~ are modified.

20. The dsRNA agent of claim 19, wherein the sense strand and the antisense strand each contain at least one 2′-O-methyl modification and at least one 2′-fluoro modification.

~~11. The dsRNA agent of any one of claims 3-10, wherein at least one of said 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'-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 glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide, and combinations thereof.~~

~~12. The dsRNA agent of claim 11, wherein the nucleotide modifications are 2'-O-methyl and/or 2'-fluoro modifications.~~

~~13. The dsRNA agent of any one of claims 1-12, wherein the region of complementarity is at least 17 nucleotides in length.~~

~~14. The dsRNA agent of any one of claims 1-13, wherein the region of complementarity is 19 to 30 nucleotides in length.~~

~~15. The dsRNA agent of claim 14, wherein the region of complementarity is 19-25 nucleotides in length.~~

~~16. The dsRNA agent of claim 15, wherein the region of complementarity is 21 to 23 nucleotides in length.~~

21. ~~17~~. The dsRNA agent of ~~any one of claims 1-16~~claim 20, wherein ~~each~~the sense strand ~~is no more than 30 nucleotides in length.~~

~~18. The dsRNA agent of any one of claims 1-17, wherein each~~and/or the antisense strand ~~is~~each independently ~~19-30 nucleotides in length.~~

~~19. The dsRNA agent of claim 18, wherein each strand is independently 19-25 nucleotides in length.~~

~~20. The dsRNA agent of claim 18, wherein each strand is independently 21-23 nucleotides in length.~~

~~21. The dsRNA agent of any one of claims 1-20, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.~~

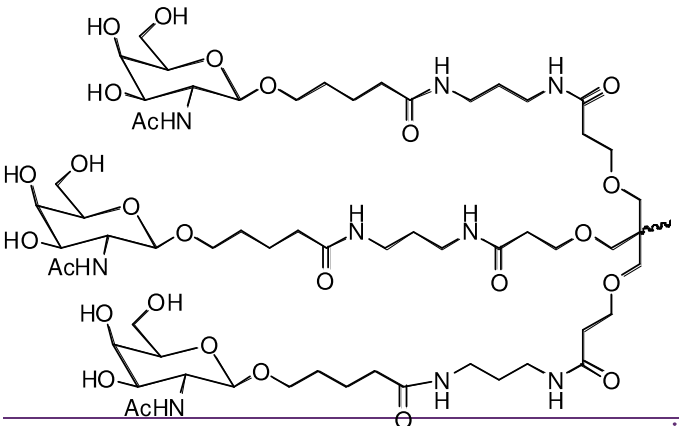
~~22. The dsRNA agent of any one of claim 21, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.~~

~~23. The dsRNA agent of any one of claims 1-6 and 11-22 further comprising a ligand.~~

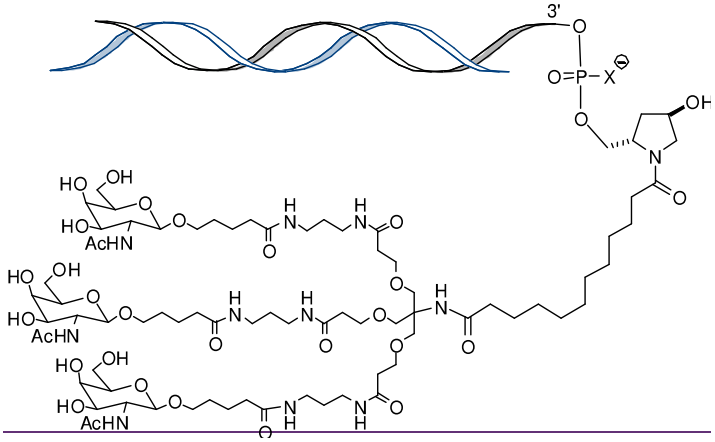
~~24. The dsRNA agent of claim 23, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.~~

~~25. The dsRNA agent of claim 7 or 24, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.~~

~~26. The dsRNA agent of claim 25, wherein the ligand is~~



27. The dsRNA agent of claim 26, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

contain 1-28. The dsRNA agent of claim 27, wherein the X is O.

29. The dsRNA agent of claim 2, wherein the region of complementarity comprises any one of the antisense sequences in any one of Tables 2, 3, 7, 8, 10, 11, or 13.

30. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein said dsRNA agent comprises a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein said dsRNA agent is represented by formula (III):

sense: 5' n_p-N_a-(X X X)$_i$-N_b-Y Y Y-N_b-(Z Z Z)$_j$-N_a-n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'-n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

31. The dsRNA agent of claim 30, wherein i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1.

32. The dsRNA agent of claim 30, wherein k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1.

33. The dsRNA agent of claim 30, wherein XXX is complementary to X′X′X′, YYY is complementary to Y′Y′Y′, and ZZZ is complementary to Z′Z′Z′.

34. The dsRNA agent of claim 30, wherein the YYY motif occurs at or near the cleavage site of the sense strand.

35. The dsRNA agent of claim 30, wherein the Y′Y′Y′ motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5' end.

36. The dsRNA agent of claim 30, wherein formula (III) is represented by formula (IIIa):

sense: 5' n_p- N_a- Y Y Y- N_a- n_q 3'

antisense: 3' n_p'- N_a'- Y′Y′Y′- N_a'- n_q' 5' (IIIa).

37. The dsRNA agent of claim 30, wherein formula (III) is represented by formula (IIIb):

sense: 5' n_p- N_a- Y Y Y- N_b- Z Z Z- N_a- n_q-3'

antisense: 3' n_p'- N_a'- Y'Y'Y'- N_b'- Z'Z'Z'- N_a'- n_q'-5' (IIIb)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

38. The dsRNA agent of claim 30, wherein formula (III) is represented by formula (IIIc):

sense: 5' n_p- N_a- X X X- N_b- Y Y Y- N_a- n_q-3'

antisense: 3' n_p'- N_a'- X'X'X'- N_b'- Y'Y'Y'- N_a'- n_q'-5' (IIIc)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

39. The dsRNA agent of claim 30, wherein formula (III) is represented by formula (IIId):

sense: 5' n_p- N_a- X X X- N_b- Y Y Y- N_b- Z Z Z- N_a- n_q-3'

antisense: 3' n_p'- N_a'- X'X'X'- N_b'- Y'Y'Y'- N_b'- Z'Z'Z'- N_a'- n_q'-5' (IIId)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides and each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 modified nucleotides.

40. The dsRNA agent of any one of claims 30-39, wherein the region of complementarity is at least 17 nucleotides in length.

41. The dsRNA agent of any one of claims 30-39, wherein the region of complementarity is 19 to 30 nucleotides in length.

42. The dsRNA agent of claim 41, wherein the region of complementarity is 19-25 nucleotides in length.

43. The dsRNA agent of claim 42, wherein the region of complementarity is 21 to 23 nucleotides in length.

44. The dsRNA agent of any one of claims 30-43, wherein each strand is no more than 30 nucleotides in length.

~~45. The dsRNA agent of any one of claims 30-43, wherein each strand is independently 19-30 nucleotides in length.~~

~~46. The dsRNA agent of any one of claims 30-45, 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' O-methyl, 2′ deoxy, 2' hydroxyl, and combinations thereof.~~

~~47. The dsRNA agent of claim 46, wherein the modifications on the nucleotides are 2′ O-methyl and/or 2′ fluoro modifications.~~

~~48. The dsRNA agent of claim any one of claims 30-46, wherein the Y′ is a 2′ O-methyl or 2' flouro modified nucleotide.~~

~~49. The dsRNA agent of any one of claims 30-48, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.~~

~~50. The dsRNA agent of any one of claims 30-49, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.~~

~~51. The dsRNA agent of any one of claims 30-50, wherein the dsRNA agent further comprises at least one~~ phosphorothioate or methylphosphonate internucleotide ~~linkage.~~

~~52. The dsRNA agent of claim 51, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3' terminus of one strand.~~

~~53. The dsRNA agent of claim 52, wherein said strand is the antisense strand.~~

~~54. The dsRNA agent of claim 52, wherein said strand is the sense strand.~~

~~55. The dsRNA agent of claim 51, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5' terminus of one strand.~~

~~56. The dsRNA agent of claim 55, wherein said strand is the antisense strand.~~

~~57. The dsRNA agent of claim 55, wherein said strand is the sense strand.~~

~~58. The dsRNA agent of claim 51, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at both the 5' and 3' terminus of one strand.~~

~~59. The dsRNA agent of claim 30, wherein the base pair at the 1 position of the 5′ end of the antisense strand of the duplex is an AU base pair.~~

~~60. The dsRNA agent of claim 30, wherein p′>0.~~

~~61. The dsRNA agent of claim 30, wherein p′=2.~~

~~62. The dsRNA agent of claim 61, wherein q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA.~~

~~63. The dsRNA agent of claim 61, wherein q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.~~

~~64. The dsRNA agent of claim 30, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.~~

~~65. The dsRNA agent of claim 30, wherein at least one n_p′ is linked to a neighboring nucleotide via a phosphorothioate linkage.~~

~~66. The dsRNA agent of claim 65, wherein all n_p′ are linked to neighboring nucleotides via phosphorothioate~~ linkages at their 5′-termini and/or 3′-termini.

~~67~~22. The dsRNA agent of claim ~~30~~21, wherein ~~all of the nucleotides of~~ :

(a) the sense strand ~~and all of the~~ comprises:

(i) four 2′-fluoro modified nucleotides at nucleotides ~~of the antisense strand comprise a modification.~~7 and 9-11, counting from the 5′-end;

~~68. The dsRNA agent of any one of claims 30-67, wherein~~(ii) seventeen 2′-O-methyl modified nucleotides at nucleotides 1-6, 8, and 12-21, counting from the ~~ligand is conjugated to~~5′-end; and

(iii) phosphorothioate linkages between nucleotides 1 and 2 and between nucleotides 2 and 3, counting from the ~~3'~~ 5′-end ~~of~~ ; and

(b) the ~~sense~~antisense strand ~~of~~comprises:

(i) three 2′-fluoro modified nucleotides at nucleotides 2, 14, and 16, counting from the ~~dsRNA agent.~~ 5′-end;

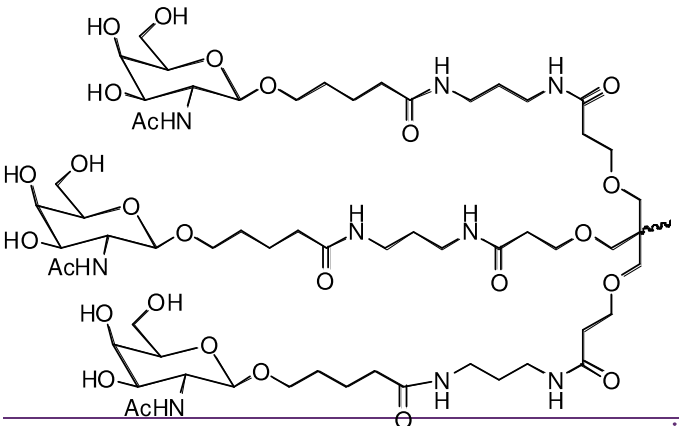
~~69~~(ii) nineteen 2′-O-methyl modified nucleotides at nucleotides 1, 3-6, 8-13, 15, and 17-23, counting from the 5′-end;

(iii) one glycol modified nucleotide at nucleotide 7, counting from the 5′-end; and

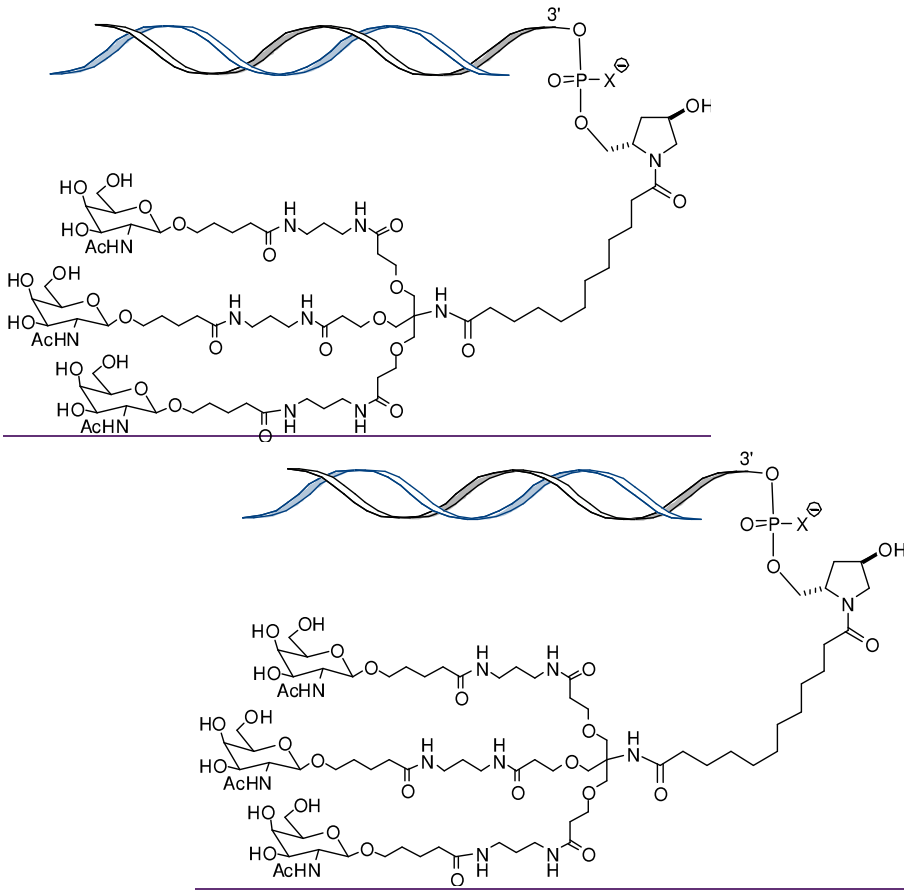
(iv) phosphorothioate linkages between nucleotides 1 and 2, between nucleotides 2 and 3, between nucleotides 21 and 22, and between nucleotides 22 and 23, counting from the 5′-end.

23. The dsRNA agent of claim ~~68~~22, wherein the sense strand is conjugated to a ligand, wherein the ligand ~~is one or more~~ comprises a multivalent galactose, an N-acetylgalactosamine ~~(GalNAc) derivatives attached through a monovalent, bivalent, or~~ , an N-acetylgalactosamine derivative, a divalent N-acetylgalactosamine, or a trivalent ~~branched linker~~N-acetylgalactosamine.

~~70~~24. The dsRNA agent of claim ~~69, wherein the ligand is~~



~~71. The dsRNA agent of claim 70~~23, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic:



and, wherein X is O ~~or S~~.

~~72. The dsRNA agent of claim 71, wherein the X is O.~~

73. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein the dsRNA agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5' n_p-N_a-(X X X)$_i$-N_b-Y Y Y-N_b-(Z Z Z)$_j$-N_a-n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′-n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p′, n_q, and n_q′, each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b′ differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

74. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein the dsRNA agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5' n_p-N_a-(X X X)$_i$-N_b-Y Y Y-N_b-(Z Z Z)$_j$-N_a-n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′-n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

75. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein the dsRNA agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5′ n_p-N_a-(X X X)$_i$-N_b-Y Y Y-N_b-(Z Z Z)$_j$-N_a-n_q 3′

antisense: 3′ n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'-n_q' 5′ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

76. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein the dsRNA agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}Y\,Y\,Y\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q' are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y';

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

77. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) in a cell, wherein the dsRNA agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HSD17B13, wherein each strand is about 14 to about 30 nucleotides in length, wherein the dsRNA agent is represented by formula (III):

sense: 5' n_p-N_a-YYY-N_a-n_q 3'

antisense: 3' n_p′-N_a′-Y′Y′Y′-N_a′-n_q′ 5' (IIIa)

wherein:

each n_p, n_q, and n_q′, each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p′ >0 and at least one n_p′ is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y′Y′Y′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

78. A double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) 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 SEQ ID NO:1 or 2 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:8 or 9,

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

~~wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5' terminus,~~

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

~~wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5' terminus and two phosphorothioate internucleotide linkages at the 3' terminus, and~~

~~wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a monovalent, bivalent or trivalent branched linker at the 3' terminus.~~

~~79. The dsRNA agent of claim 78, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.~~

~~80. The dsRNA agent of any one of claims 2, 30, and 73-79 wherein the region of complementarity comprises any one of the antisense sequences listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13.~~

~~81. The dsRNA agent of any one of claims 1-80, wherein the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of the nucleotide sequences of any one of the agents listed in any one of Tables 2, 3, 7, 8, 10, 11, or 13.~~

~~82. A cell containing the dsRNA agent of any one of claims 1-81.~~

~~83. A vector encoding at least one strand of the dsRNA agent of any one of claims 1-81.~~

~~84.~~25. A pharmaceutical composition for inhibiting expression of ~~the 17β-hydroxysteroid dehydrogenases Type 13 (HSD17B13)~~a gene encoding 17β-hydroxysteroid dehydrogenase type 13 (HSD17B13) comprising the dsRNA agent of ~~any one of claims~~claim 1-~~81~~.

~~85~~26. The pharmaceutical composition of claim ~~84~~25, wherein the dsRNA agent is ~~formulated~~ in ~~an unbuffered~~a buffered solution.

~~86~~27. The pharmaceutical composition of claim ~~85~~26, wherein the ~~unbuffered~~buffered solution ~~is~~comprises acetate, citrate, prolamine, carbonate, phosphate, phosphate buffered saline, or ~~water~~any combination thereof.

28.

~~87. The~~A pharmaceutical composition ~~of claim 84, wherein the agent is formulated with a buffered solution~~for inhibiting expression of a gene encoding 17β-hydroxysteroid dehydrogenase type 13 (HSD17B13) comprising the dsRNA agent of claim 24.

~~88~~29. The pharmaceutical composition of claim ~~87~~28, wherein ~~said~~the dsRNA agent is in a buffered solution.

30. The pharmaceutical composition of claim 29, wherein the buffered solution comprises acetate, citrate, prolamine, carbonate, ~~or~~ phosphate, phosphate buffered saline, or any combination thereof.

~~89. The pharmaceutical composition of claim 87, wherein the buffered solution is phosphate buffered saline (PBS).~~

~~90. A method of inhibiting 17β hydroxysteroid dehydrogenases type 13 (HSD17B13) expression in a cell, the method comprising contacting the cell with the agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, thereby inhibiting expression of HSD17B13 in the cell.~~

~~91. The method of claim 90, wherein said cell is within a subject.~~

~~92. The method of claim 91, wherein the subject is a human.~~

~~93. The method of any one of claims 90-92, wherein the HSD17B13 expression is inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of detection of HSD17B13 expression.~~

94. The method of claim 93, wherein the human subject suffers from an HSD17B13-associated disease, disorder, or condition.

95. The method of claim 94, wherein the HSD17B13-associated disease, disorder, or condition is a chronic fibro-inflammatory liver disease.

96. The method of claim 95, wherein the chronic fibro-inflammatory liver disease is associated with the accumulation and/or exapansion of lipid droplets in the liver.

97. The method of claim 95, wherein the chronic fibro-inflammatory liver disease is selected from the group consisting of inflammation of the liver, liver fibrosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver, alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug induced liver injury, and hepatocellular necrosis.

98. A method of inhibiting the expression of HSD17B13 in a subject, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, thereby inhibiting the expression of HSD17B13 in said subject.

99. A method of treating a subject suffering from an HSD17B13-associated disease, disorder, or condition, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, thereby treating the subject suffering from an HSD17B13-associated disease, disorder, or condition.

100. A method of preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene, comprising administering to the subject a prophylactically effective amount of the agent of any one of claims 1-31, or a pharmaceutical composition of any one of claims 34-39, thereby preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene.

101. A method of reducing the risk of developing chronic liver disease in a subject having steatosis, the method comprising administering to the subject a therapeutically effective amount of

~~the dsRNA agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, thereby reducing the risk of developing chronic liver disease in the subject having steatosis.~~

~~102. A method of inhibiting the progression of steatosis to steatohepatitis in a subject suffering from steatosis, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, thereby inhibiting the progression of steatosis to steatohepatitis in the subject.~~
~~103. A method of inhibiting the accumulation of lipid droplets in the liver of a subject suffering from an HSD17B13-associated disease, disorder, or condition, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby inhibiting the accumulation of fat in the liver of the subject suffering from an HSD17B13-associated disease, disorder, or condition.~~

~~104. A method of treating a subject suffering from an HSD17B13-associated disease, disorder, or condition, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby treating the subject suffering from an HSD17B13-associated disease, disorder, or condition.~~

~~105. A method of preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene, comprising administering to the subject a prophylactically effective amount of the agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby preventing at least one symptom in a subject having a disease, disorder or condition that would benefit from reduction in expression of an HSD17B13 gene.~~

~~106. A method of reducing the risk of developing chronic liver disease in a subject having steatosis, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a~~

dsRNA agent targeting a PNPLA3 gene, thereby reducing the risk of developing chronic liver disease in the subject having steatosis.

107. A method of inhibiting the progression of steatosis to steatohepatitis in a subject suffering from steatosis, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-81, or a pharmaceutical composition of any one of claims 84-89, and a dsRNA agent targeting a PNPLA3 gene or a pharmaceutical composition comprising a dsRNA agent targeting a PNPLA3 gene, thereby inhibiting the progression of steatosis to steatohepatitis in the subject.

108. The method of any one of claims 91-107, wherein the administration of the dsRNA agent or the pharmaceutical composition to the subject causes a decrease in HSD17B13 enzymatic activity, a decrease in HSD17B13 protein accumulation, a decrease in PNPLA3 enzymatic activity, a decrease in PNPLA3 protein accumulation, and/or a decrease in accumulation of fat and/or expansion of lipid droplets in the liver of a subject.

109. The method of claimany one of claims 99-108, wherein the HSD17B13-associated disease, disorder, or condition is a chronic fibro-inflammatory liver disease.

110. The method of claim 109, wherein the chronic fibro-inflammatory liver disease is associated with the accumulation and/or exapansion of lipid droplets in the liver.

111. The method of claim 109, wherein the chronic fibro-inflammatory liver disease is selected from the group consisting of accumulation of fat in the liver, inflammation of the liver, liver fibrosis, fatty liver disease (steatosis), nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis of the liver, alcoholic steatohepatitis (ASH), alcoholic liver diseases (ALD), HCV-associated cirrhosis, drug-induced liver injury, and hepatocellular necrosis.

112. The method of claim 111, wherein the chronic fibro-inflammatory liver disease is nonalcoholic steatohepatitis (NASH).

113. The method of any one of claims 91-112, wherein the subject is obese.

114. The method of any one of claims 91-113, further comprising administering an additional therapeutic to the subject.

115. The method of any one of claims 91-114, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

116. The method of any one of claims 91-115, wherein the agent is administered to the subject intravenously, intramuscularly, or subcutaneously.

117. The method of any one of claims 91-116, further comprising determining, the level of HSD17B13 in the subject.

118. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 17β-hydroxysteroid dehydrogenases type 13 (HSD17B13) 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 a nucleotide sequence of any one of the agents in any one of Tables 2, 3, 7, 8, 10, 11, or 13 and the antisense strand comprises a nucleotide sequence of any one of the agents in any one of Tables 2, 3, 7, 8, 10, 11,or 13,
wherein substantially all of the nucleotide of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and
wherein the dsRNA agent is conjugated to a ligand.