

CLAIMS

1. A double stranded RNAi oligonucleotide (dsRNAi) capable of inhibiting the protein expression of MARC1, wherein said dsRNAi comprises a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, and wherein the sense and antisense strands are selected from the group consisting of
 - (i) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1543 and 1579, respectively;
 - (ii) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1560 and 1596, respectively;
 - (iii) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1568 and 1604, respectively; and
 - (iv) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1553 and 1589, respectively.
2. The double stranded RNAi oligonucleotide (dsRNAi) of claim 1, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1543 and 1579, respectively.
3. The double stranded RNAi oligonucleotide (dsRNAi) of claim 1, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1560 and 1596, respectively.
4. The double stranded RNAi oligonucleotide (dsRNAi) of claim 1, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1568 and 1604, respectively.
5. The double stranded RNAi oligonucleotide (dsRNAi) of claim 1, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1553 and 1589, respectively.
6. The double stranded RNAi oligonucleotide of claim 1, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein

(i) S1 is complementary to S2, wherein S1 and S2 are 6 nucleotides in length; and
(ii) L forms a loop between S1 and S2 and wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1681).

7. The double stranded RNAi oligonucleotide of claim 2, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein

(i) S1 is complementary to S2, wherein S1 and S2 are 6 nucleotides in length; and
(ii) L forms a loop between S1 and S2 and wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1681).

8. The double stranded RNAi oligonucleotide of claim 6, comprising one or more targeting ligands conjugated to one or more nucleotides of the loop (L), wherein the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, wherein the targeting ligands are the same or different; and the targeting ligand is a hepatocyte targeting ligand comprising a N-acetylgalactosamine (GalNAc) moiety.

9. The double stranded RNAi oligonucleotide of claim 8, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.

10. The double stranded RNAi oligonucleotide of claim 8, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

11. The double stranded RNAi oligonucleotide of claim 10,
comprising at least one modified nucleotide and said modified nucleotide comprises a 2'-modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid.

12. The double stranded RNAi oligonucleotide of claim 11, wherein all nucleotides of the oligonucleotide are modified, wherein the modification is 2'-fluoro and 2'-O-methyl.

13. The double stranded RNAi oligonucleotide of claim 12, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein positions 8-11 comprise a

2'-fluoro modification; the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', and wherein positions 2, 3, 4, 5, 7, 10, and 14 comprise a 2'-fluoro modification and the remaining nucleotides comprise a 2'-O-methyl modification.

14. The double stranded RNAi oligonucleotide of claim 13, comprising at least one modified internucleotide linkage, wherein said internucleotide linkage is a phosphorothioate linkage, and wherein

(a) the antisense strand comprises a phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, wherein positions are numbered 1-4 from 5' to 3'; and/or

(b) the antisense strand is 22 nucleotides in length, and wherein the antisense strand comprises a phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, wherein positions are numbered 1-22 from 5' to 3'.

15. The double stranded RNAi oligonucleotide of claim 14, wherein the antisense strand comprises a phosphorylated nucleotide at the 5' terminus, wherein the phosphorylated nucleotide is uridine,

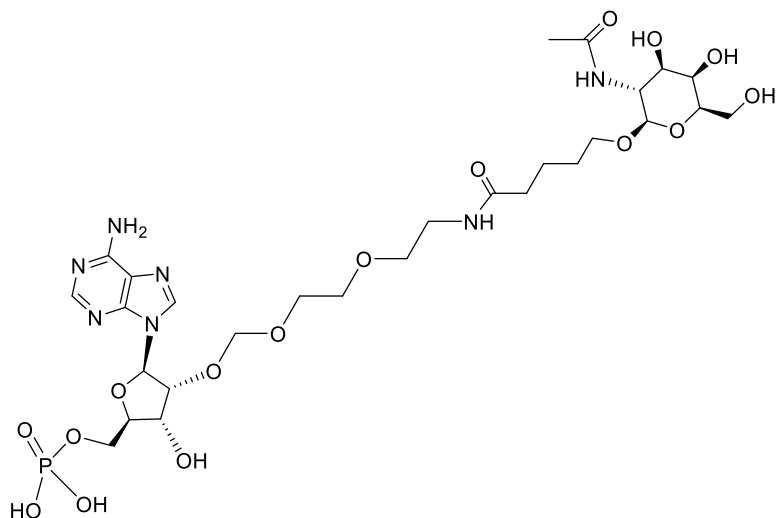
16. The double stranded RNAi oligonucleotide of claim 14, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

17. The double stranded RNAi oligonucleotide of claim 16, wherein the 4'-phosphate analog comprises 5'-methoxyphosphonate-4'-oxy.

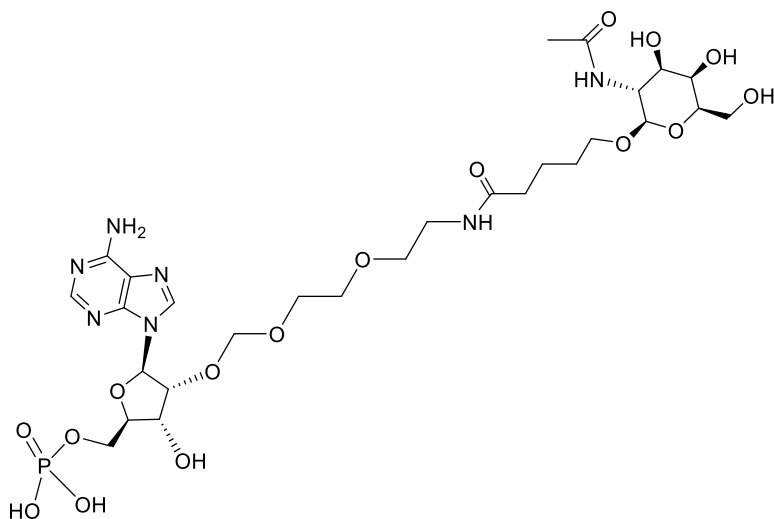
18. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting the expression of MARC1, wherein said dsRNAi comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein

(i) the sense strand comprises the sequence and all of the modifications of 5'-mGs-mG-mC-mU-mA-mG-mA-fG-fA-fA-fG-mA-mA-mA-mG-mU-mU-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1615), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fA-fA-mC-fU-

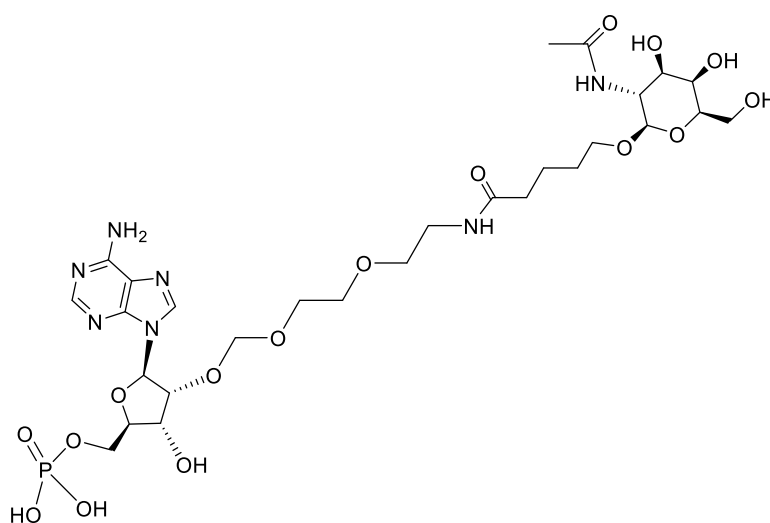
mU-mU-fC-mU-mU-mC-fU-mC-mU-mA-mG-mC-mCs-mGs-mG-3' (SEQ ID NO: 1651), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



(ii) the sense strand comprises the sequence and all of the modifications of 5'-mAs-mG-mA-mA-mC-mG-mA-fA-fA-fG-fU-mU-mA-mU-mA-mU-mG-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1632), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fCs-fC-fA-mU-fA-mU-mA-fA-mC-mU-mU-fU-mC-mG-mU-mU-mC-mUs-mGs-mG-3' (SEQ ID NO: 1668), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



(iii) the sense strand comprises the sequence and all of the modifications of 5'-mAs-mA-mG-mU-mU-mG-mA-fC-fU-fA-fA-mA-mC-mU-mU-mG-mA-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1640), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fU-fC-mA-fA-mG-mU-fU-mU-mA-mG-fU-mC-mA-mA-mC-mU-mUs-mGs-mG-3' (SEQ ID NO: 1676), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



or

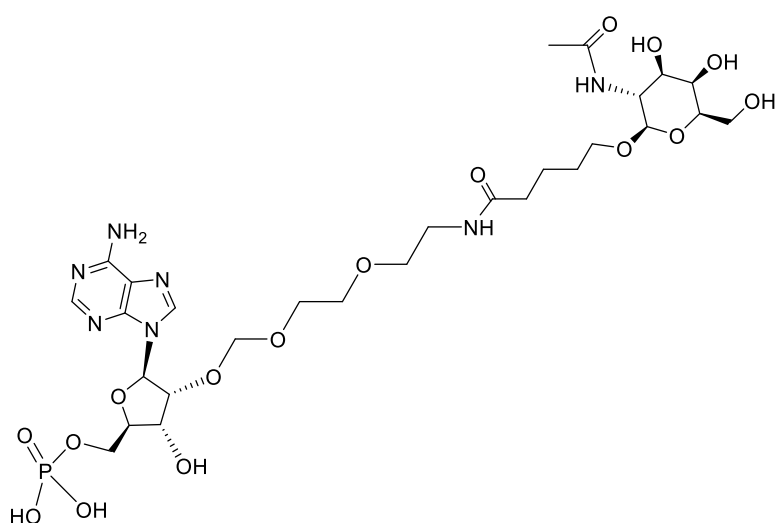
(iv) the sense strand comprises the sequence and all of the modifications of 5'-mUs-mG-mU-mG-mA-mA-mU-fA-fA-fA-fU-mG-mG-mA-mA-mG-mC-mU-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1625), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fAs-fG-fC-mU-fU-mC-mC-fA-mU-mU-mU-fA-mU-mU-mC-mA-mC-mAs-mGs-mG-3' (SEQ ID NO: 1661), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =

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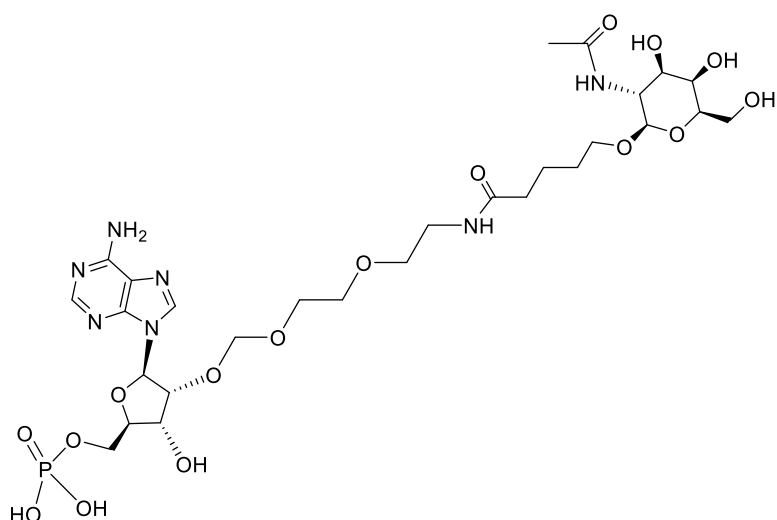


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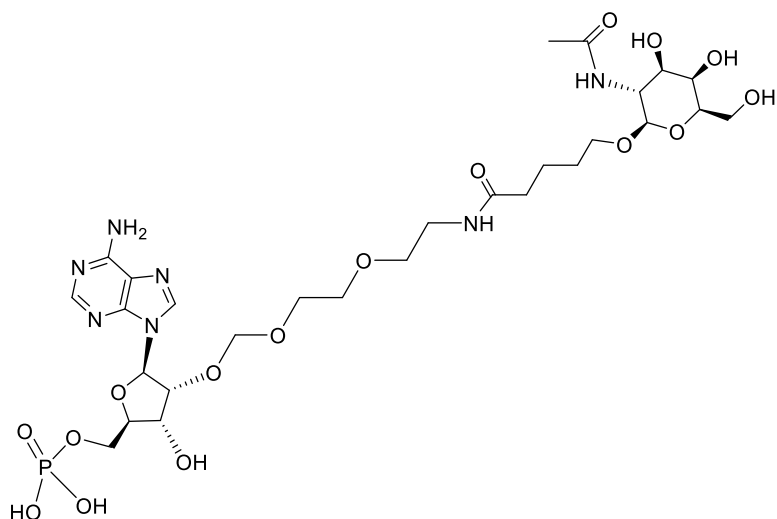
mA-fA-fA-fG-fU-mU-mA-mU-mA-mU-mG-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1632), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fCs-fC-fA-mU-fA-mU-mA-fA-mC-mU-mU-fU-mC-mG-mU-mU-mC-mUs-mGs-mG-3' (SEQ ID NO: 1668), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



21. The double stranded RNAi oligonucleotide (dsRNAi) of claim 18, wherein the sense strand comprises the sequence and all of the modifications of 5'-mAs-mA-mG-mU-mU-mG-mA-fC-fU-fA-fA-mA-mC-mU-mU-mG-mA-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1640), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fU-fC-mA-fA-mG-mU-fU-mU-mA-mG-fU-mC-mA-mA-mC-mU-mUs-mGs-mG-3' (SEQ ID NO: 1676), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



22. The double stranded RNAi oligonucleotide (dsRNAi) of claim 18, wherein the sense strand comprises the sequence and all of the modifications of 5'-mUs-mG-mU-mG-mA-mA-mU-fA-fA-fA-fU-mG mG-mA-mA-mG-mC-mU-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1625), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fAs-fG-fC-mU-fU-mC-mC-fA-mU-mU-mU-fA-mU-mU-mC-mA-mC-mAs-mGs-mG-3' (SEQ ID NO: 1661), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



23. A pharmaceutical composition comprising the double stranded RNAi oligonucleotide of claim 18, and a pharmaceutically acceptable carrier, delivery agent or excipient.

24. A pharmaceutical composition comprising the double stranded RNAi oligonucleotide of claim 19, and a pharmaceutically acceptable carrier, delivery agent or excipient.
25. Use of a therapeutically effective amount of the double stranded RNAi oligonucleotide of claim 18 in the manufacture of a medicament for the treatment of a disease or condition associated with MARC1 expression in hepatocytes selected from the group consisting of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and alcoholic steatohepatitis (ASH).
26. Use of a therapeutically effective amount of the double stranded RNAi oligonucleotide of claim 19 in the manufacture of a medicament for the treatment of a disease or condition associated with MARC1 expression in hepatocytes selected from the group consisting of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and alcoholic steatohepatitis (ASH).
27. A kit comprising the double stranded RNAi oligonucleotide of claim 19, a pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with MARC1 expression selected from the group consisting of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and alcoholic steatohepatitis (ASH).