

CLAIMS:

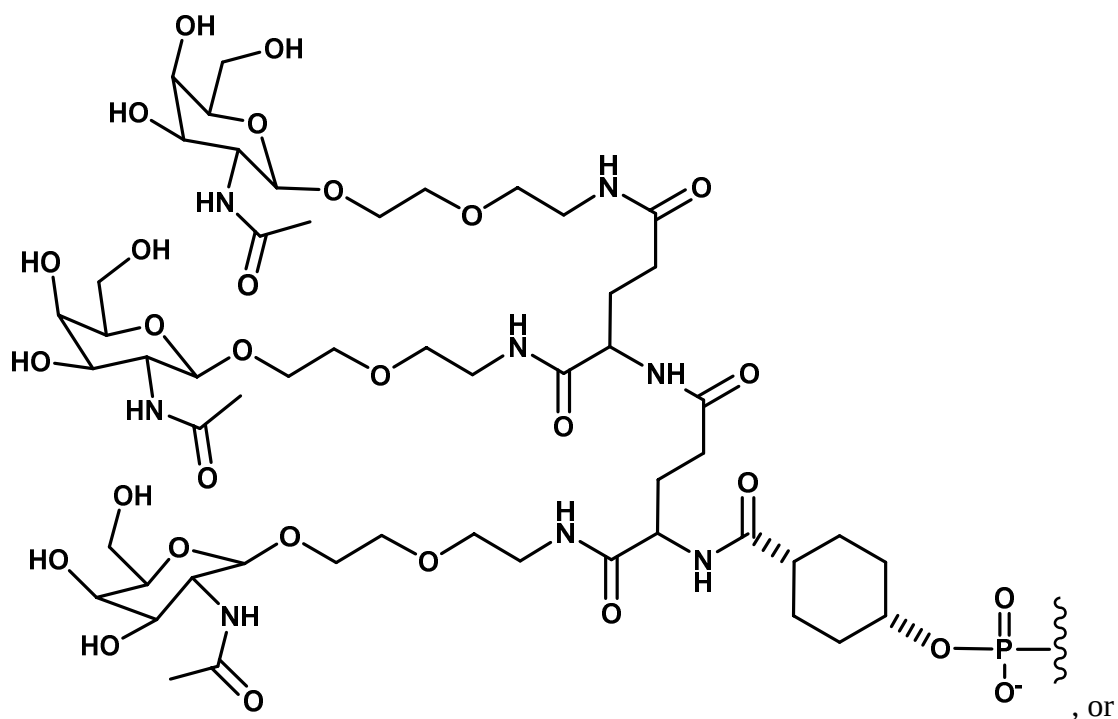
1. A RNAi agent for inhibiting expression of a PNPLA3 gene, comprising:
an antisense strand comprising the modified nucleotide sequence
usUfsasGfuUfaGfgUfgAfaAfaAfgGfuGfsu (SEQ ID NO:95),
wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage; and
a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.
2. The RNAi agent of claim 1, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from the sense strand sequence sacaccuuuUfUfCfaccuaacuaas (SEQ ID NO:136), and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.
3. The RNAi agent of claim 1, wherein at least one nucleotide of the sense strand of the RNAi agent is a modified nucleotide or includes a modified internucleoside linkage.
4. The RNAi agent of any one of claims 1-3, wherein all or substantially all of the nucleotides of the sense strand of the RNAi agent are modified nucleotides.
5. The RNAi agent of any one of claims 3-4, wherein the modified nucleotide is selected from the group consisting of: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2',3'-seco nucleotide mimic, locked nucleotide, 2'-F-arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted 2'-O-methyl nucleotide, inverted 2'-deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, vinyl phosphonate containing nucleotide, cyclopropyl phosphonate containing nucleotide, and 3'-O-methyl nucleotide.

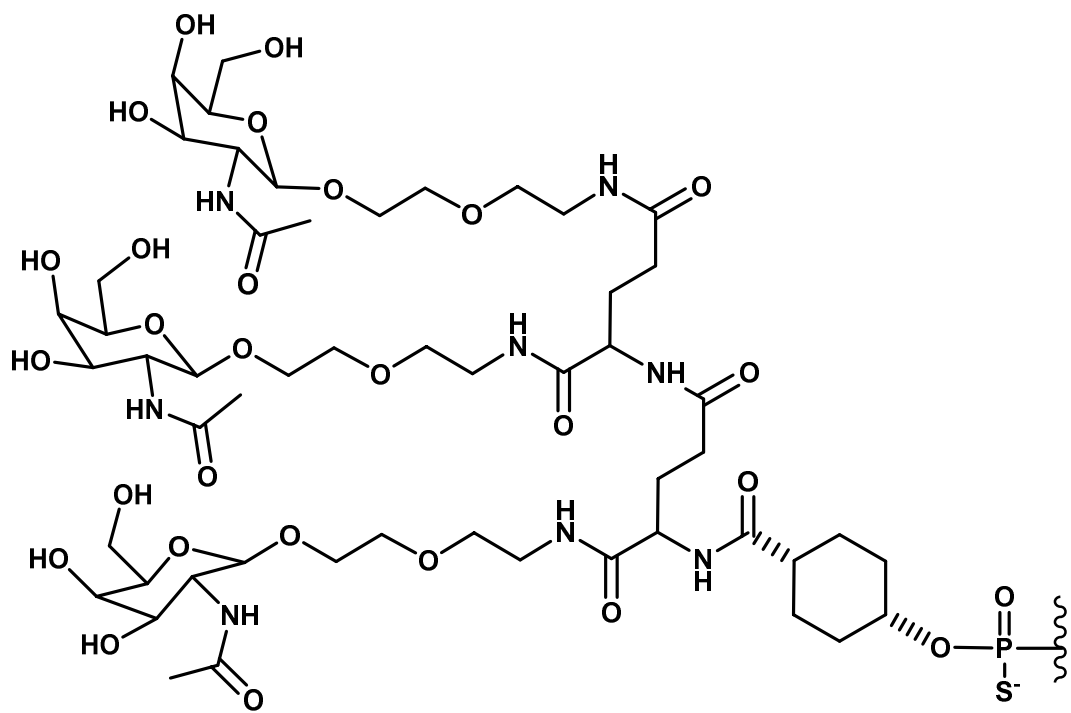
6. The RNAi agent of claim 4, wherein all or substantially all of the modified nucleotides are 2'-O-methyl nucleotides, 2'-fluoro nucleotides, or combinations thereof.
7. The RNAi agent of any one of claims 1-5, wherein the antisense strand consists of, consists essentially of, or comprises the modified nucleotide sequence
usUfsasGfuUfaGfgUfgAfaAfaAfgGfuGfsu (SEQ ID NO: 95) and the sense strand
comprises the modified nucleotide sequence sacaccuuuUfUfCfaccuaacuaas (SEQ ID NO: 136).
8. The RNAi agent of any one of claims 1-5, wherein the sense strand consists of, consists essentially of, or comprises the nucleotide sequence of any of the modified sense strand sequences of
sa_2NcaccuuuUfUfCfaccuaacuaas (SEQ ID NO: 164),
acaccuuuUfUfCfaccuaacua_2Nas (SEQ ID NO: 165),
sa_2NcaccuuuUfUfCfaccuaacua_2Nas (SEQ ID NO: 166), and
cAfcCfuUfuUfUfCfaccuaacuaas (SEQ ID NO: 167),
wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s represents a phosphorothioate linkage, and 2N represents 2'-O-methyl-2-aminoadenosine-3'-phosphate
.
9. The RNAi agent of claim 1, wherein the antisense strand comprises the modified nucleotide sequence usUfsasGfuUfaGfgUfgAfaAfaAfgGfuGfsu (SEQ ID NO: 95) and the sense strand comprises the modified nucleotide sequence sacaccuuuUfUfCfaccuaacuaas (SEQ ID NO: 136).
10. The RNAi agent of any one of claims 1-9, wherein the RNAi agent is linked to a targeting ligand.
11. The RNAi agent of claim 10, wherein the targeting ligand comprises N-acetyl-galactosamine.

12. The RNAi agent of claim 10 or 11, wherein the targeting ligand comprises the structure of (NAG37) or (NAG37)s.
13. The RNAi agent of any one of claims 10-12, wherein the targeting ligand is linked to the sense strand.
14. The RNAi agent of claim 13, wherein the targeting ligand is linked to the 5' terminal end of the sense strand.
15. The RNAi agent of any one of claims 1-14, wherein the sense strand is between 18 and 30 nucleotides in length.
16. The RNAi agent of claim 15, wherein the sense strand is between 18 and 27 nucleotides in length.
17. The RNAi agent of claim 16, wherein the sense strand is between 18 and 24 nucleotides in length.
18. The RNAi agent of claim 17, wherein the sense strand is 21 nucleotides in length.
19. The RNAi agent of any one of claims 15-18, wherein the RNAi agent has two blunt ends.
20. The RNAi agent of any one of claims 1-19, wherein the sense strand comprises one or two terminal caps.
21. The RNAi agent of any one of claims 1-20, wherein the sense strand comprises one or two inverted abasic residues.

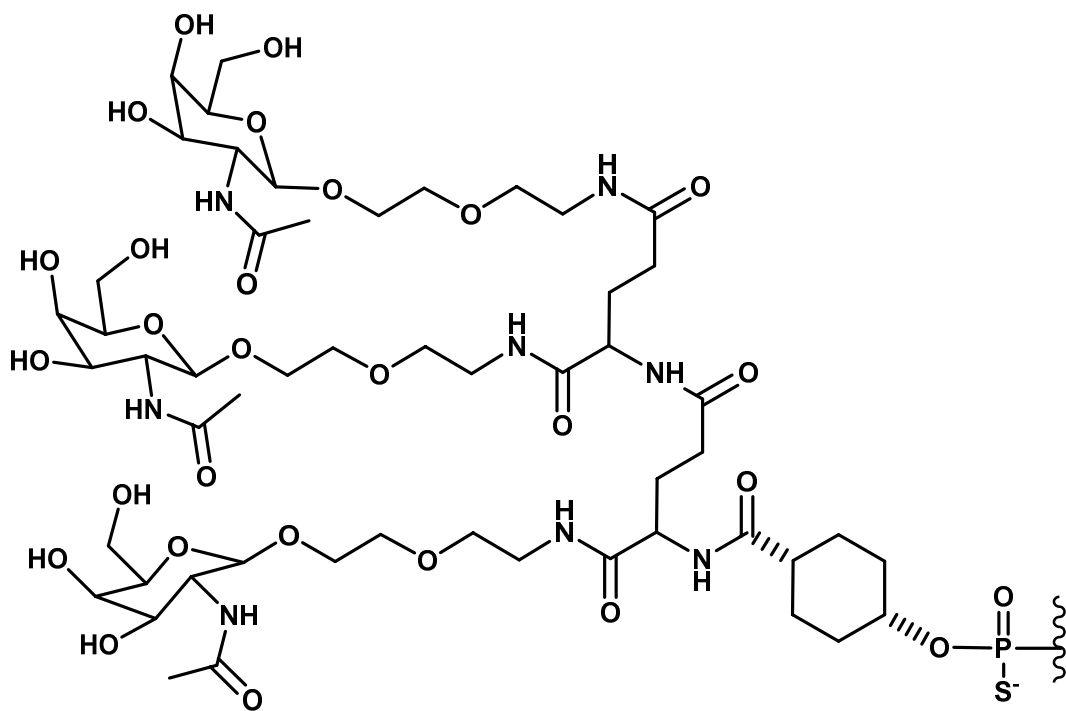
22. The RNAi agent of claim 1, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex sequence with SEQ ID NOs: (95 and 136); (95 and 164); (95 and 165); (95 and 166); and/or (95 and 167).
23. The RNAi agent of any one of claims 1-22, wherein the sense strand further includes inverted abasic residues at the 3' terminal end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both.
24. The RNAi agent of claim 1, comprising an antisense strand that comprises, consists of, or consists essentially of a modified nucleotide sequence
usUfsasGfuUfaGfgUfgAfaAfaAfgGfuGfsu (SEQ ID NO: 95);
wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s represents a phosphorothioate linkage; and wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides.
25. The RNAi agent of claim 1, wherein the sense strand consists of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the nucleotide sequences of
sacaccuuuUfUfCfaccuaacuaas (SEQ ID NO: 136)
sa_2NcaccuuuUfUfCfaccuaacuaas (SEQ ID NO: 164),
acaccuuuUfUfCfaccuaacua_2Nas (SEQ ID NO: 165),
sa_2NcaccuuuUfUfCfaccuaacua_2Nas (SEQ ID NO: 166), and
cAfcCfuUfuUfUfCfaccuaacuaas (SEQ ID NO: 167);
wherein a, c, g, i, and u represent 2'-O-methyl adenosine, cytidine, guanosine, inosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s represents a phosphorothioate linkage; and 2N represents 2'-O-methyl-2-aminoadenosine-3'-phosphate.
26. The RNAi agent of any one of claims 24-25, wherein the sense strand further includes inverted abasic residues at the 3' terminal end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both.

27. The RNAi agent of any one of claims 24-26, wherein the sense strand of the RNAi agent is linked to a targeting ligand.
28. The RNAi agent of claim 27, wherein the targeting ligand has affinity for the asialoglycoprotein receptor.
29. The RNAi agent of claim 28, wherein the targeting ligand comprises N-acetyl-galactosamine.
30. The RNAi agent of claim 29, wherein the targeting ligand comprises:





31. The RNAi agent of claim 1, wherein the antisense strand consists of the modified nucleotide sequence of SEQ ID NO: 95, and the sense strand consists of the modified nucleotide sequence of SEQ ID NO: 136;
 wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s is a phosphorothioate linkage; (invAb) is an inverted abasic deoxyribose residue; and (NAG37)s has the following chemical structure:



32. A composition comprising the RNAi agent of any one of claims 1-31, wherein the composition further comprises a pharmaceutically acceptable excipient.
33. An *in vitro* method for inhibiting expression of a PNPLA3 gene in a cell, the method comprising introducing into a cell an effective amount of an RNAi agent of any one of claims 1-31 or the composition of claim 32.
34. The method of claim 33, wherein the PNPLA3 gene expression is inhibited by at least 30%.
35. Use of the composition of claim 32 in the manufacture of a medicament for the treatment of a PNPLA3-related disease or disorder, wherein a therapeutically effective amount of the medicament is to be administered to a human subject in need thereof.
36. The use of claim 35, wherein the disease is NAFLD, NASH, hepatic fibrosis, alcoholic fatty liver disease, or cirrhosis.

37. The use of claim 35 or 36, wherein the RNAi agent is to be administered at a dose of 0.05 mg/kg to 5.0 mg/kg of body weight of the human subject.
38. The use of any one of claims 35-37, wherein the RNAi agent is to be administered in two or more doses.
39. The RNAi agent of any one of claims 1-31 or the composition according to claim 32, for use in the treatment of a disease, disorder, or symptom that is mediated at least in part PNPLA3 gene expression.
40. Use of the RNAi agent of any one of claims 1-31 or the composition according to claim 32, for the preparation of a pharmaceutical compositions for treating a disease, disorder, or symptom that is mediated at least in part by PNPLA3 gene expression.
41. The use according to claim 40, wherein the symptom is cirrhosis of the liver.
42. The use according to any one of claims 40 to 41, wherein the disease is NAFLD, NASH, hepatic fibrosis, or an alcoholic or non-alcoholic liver disease such as cirrhosis.
43. Use according to any one of claims 40 to 41, wherein the RNAi agent is to be administered at a dose of 0.05 mg/kg to 5.0 mg/kg of body weight of the human subject.