

CLAIMS:

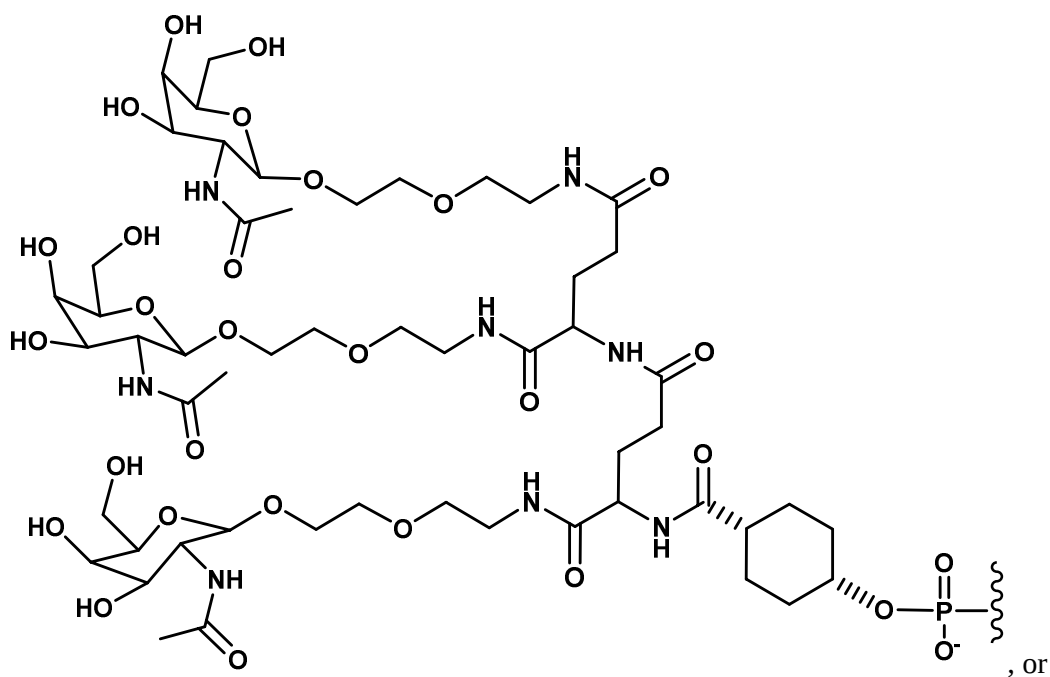
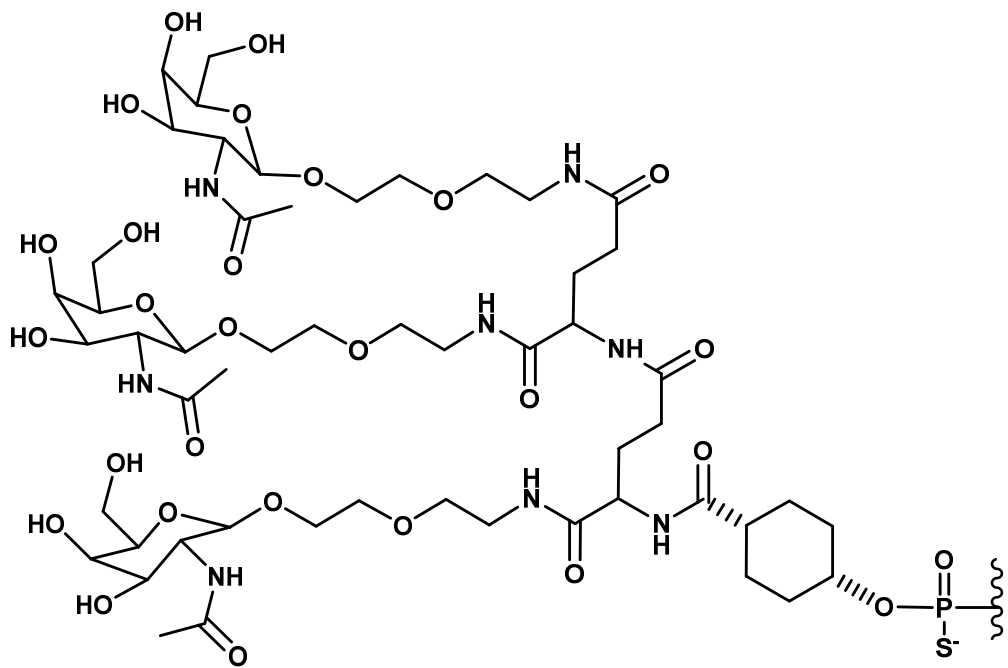
1. An RNAi agent for inhibiting expression of a PNPLA3 gene, comprising:
 - an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences of SEQ ID NOs: 46-60, 176, 181 and 188 ; and
 - a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.
2. The RNAi agent of claim 1, wherein the antisense strand comprises nucleotides 2-18 of any one of the sequences of SEQ ID NOs: 46-60, 176, 181 and 188.
3. The RNAi agent of claim 1 or claim 2, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sense strand sequences of SEQ ID NOs: 2, 3, 4, 9-20, 214, 219 and 220, and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.
4. The RNAi agent of any one of claims 1-3, wherein at least one nucleotide of the RNAi agent is a modified nucleotide or includes a modified internucleoside linkage.
5. The RNAi agent of any one of claims 1-3, wherein all or substantially all of the nucleotides of the sense and/or antisense strand of the RNAi agent are modified nucleotides.
6. The RNAi agent of any one of claims 4-5, 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.

7. The RNAi agent of claim 5, wherein all or substantially all of the modified nucleotides are 2'-O-methyl nucleotides, 2'-fluoro nucleotides, or combinations thereof.
8. The RNAi agent of any one of claims 1-7, wherein the antisense strand consists of, consists essentially of, or comprises the nucleotide sequence of any one of the modified antisense strand sequences of SEQ ID NOs: 90, 95 and 102.
9. The RNAi agent of any one of claims 1-8, wherein the sense strand consists of, consists essentially of, or comprises the nucleotide sequence of any of the modified sense strand sequences of SEQ ID NOs: 131, 136 and 137.
10. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence of any one of the modified sequences of SEQ ID NOs: 90, 95 and 102 and the sense strand comprises the nucleotide sequence of any one of the modified sequences of SEQ ID NOs: 131, 136 and 137.
11. The RNAi agent of any one of claims 1-10, wherein the RNAi agent is linked to a targeting ligand.
12. The RNAi agent of claim 11, wherein the targeting ligand comprises N-acetyl-galactosamine.
13. The RNAi agent of claim 11 or 12, wherein the targeting ligand comprises the structure of (NAG37) or (NAG37)s.
14. The RNAi agent of any one of claims 11-13, wherein the targeting ligand is linked to the sense strand.
15. The RNAi agent of claim 14, wherein the targeting ligand is linked to the 5' terminal end of the sense strand.

16. The RNAi agent of any one of claims 1-15, wherein the sense strand is between 18 and 30 nucleotides in length, and the antisense strand is between 18 and 30 nucleotides in length.
17. The RNAi agent of claim 16, wherein the sense strand and the antisense strand are each between 18 and 27 nucleotides in length.
18. The RNAi agent of claim 17, wherein the sense strand and the antisense strand are each between 18 and 24 nucleotides in length.
19. The RNAi agent of claim 18, wherein the sense strand and the antisense strand are each 21 nucleotides in length.
20. The RNAi agent of any one of claims 16-19, wherein the RNAi agent has two blunt ends.
21. The RNAi agent of any one of claims 1-20, wherein the sense strand comprises one or two terminal caps.
22. The RNAi agent of any one of claims 1-~~22~~21, wherein the sense strand comprises one or two inverted abasic residues.
23. 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: (176 and 214); (90 and 131); (181 and 219); (95 and 136); (188 and 220) and/or (102 and 137).
24. The RNAi agent of any one of claims 1-23, 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.
25. The RNAi agent of claim 1, comprising an antisense strand that comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the nucleotide sequences of SEQ ID NOs: 90, 95 and 102;

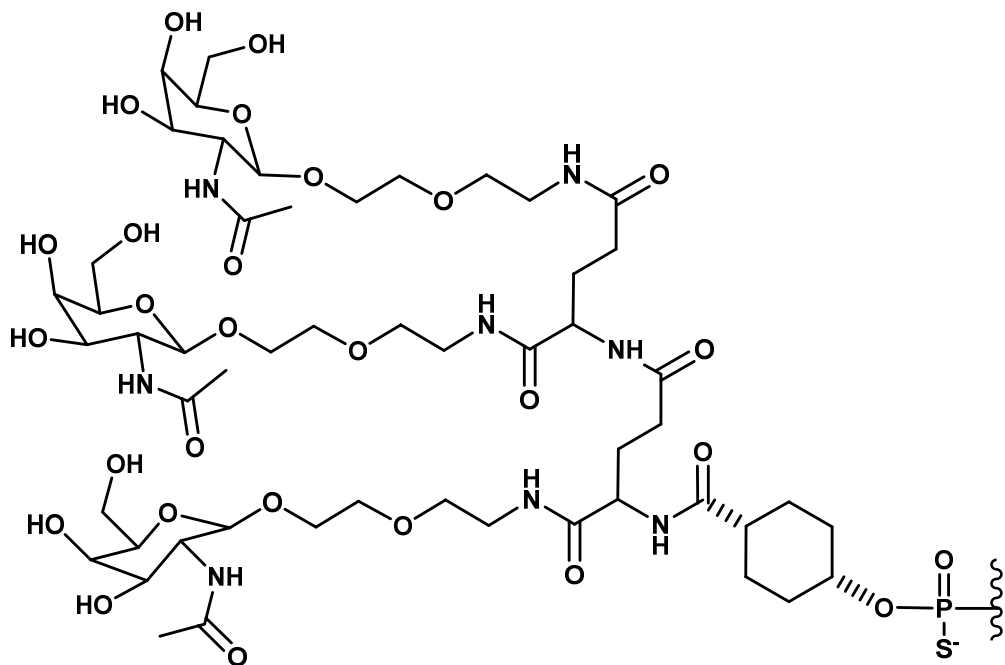
wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; s represents a phosphorothioate linkage; and wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides.

26. The RNAi agent of claim 1, wherein the sense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the nucleotide sequences of SEQ ID NOs: 214, 219 and 256; 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 wherein all or substantially all of the nucleotides on the antisense strand are modified nucleotides.
27. The RNAi agent of any one of claims 24-26, 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.
28. The RNAi agent of any one of claims 24-27, wherein the sense strand of the RNAi agent is linked to a targeting ligand.
29. The RNAi agent of claim 28, wherein the targeting ligand has affinity for the asialoglycoprotein receptor.
30. The RNAi agent of claim 29, wherein the targeting ligand comprises N-acetyl-galactosamine.
31. The RNAi agent of claim 1, wherein the targeting ligand comprises:



32. The RNAi agent of claim 1, wherein the antisense strand consists of the modified nucleotide sequence of SEQ ID NOs: 90, 95 and 102, and the sense strand consists of the modified nucleotide sequence of SEQ ID NOs: 131, 136 and 137;

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:



33. A composition comprising the RNAi agent of any one of claims 1-32, wherein the composition further comprises a pharmaceutically acceptable excipient.
34. 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 1-32 or the composition of claim 33.
- ~~35. The method of claim 34, wherein the cell is within a subject.~~
- ~~36. The method of claim 35, wherein the subject is a human subject.~~
35. The method of ~~any one of~~ claims 34-36, wherein the PNPLA3 gene expression is inhibited by at least about 30%.
- ~~37.~~

~~38.36. A method of treating a PNPLA3-related disease or disorder, the method comprising administering to a human subject in need thereof a therapeutically effective amount of the composition of claim 33~~Use of the composition of claim 33 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.

~~39.37. The method use of claim 3836,~~ wherein the disease is NAFLD, NASH, hepatic fibrosis, alcoholic fatty liver disease, or cirrhosis.

~~40.38. The method use of any one of claims 34-3936 or 37,~~ wherein the RNAi agent is to be administered at a dose of about 0.05 mg/kg to about 5.0 mg/kg of body weight of the human subject.

~~41.39. The method use of any one of claims 3436-3840,~~ wherein the RNAi agent is to be administered in two or more doses.

~~42.40. Use of~~The RNAi agent of any one of claims 1-32 or the composition according to claim 33, for use in the treatment of a disease, disorder, or symptom that is mediated at least in part PNPLA3 gene expression.

~~43. Use according to claim 42, wherein the symptom is cirrhosis of the liver.~~

41. Use of the RNAi agent of any one of claims 1-32 or the composition according to claim 33, 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.

44.42. The use according to claim 41, wherein the symptom is cirrhosis of the liver.

~~45.43. Use~~The use according to any one of claims ~~42-41~~ to ~~424~~, wherein the disease is NAFLD, NASH, hepatic fibrosis, or an alcoholic or non-alcoholic liver disease such as cirrhosis.

46.44. Use according to any one of claims ~~42-41~~ to 425, wherein the RNAi agent is to be administered at a dose of about 0.05 mg/kg to about 5.0 mg/kg of body weight of the human subject.