

CLAIMS

1. An RNAi agent for inhibiting the expression of an alpha-1 antitrypsin (AAT) gene comprising:

- (a) an antisense strand that comprises the nucleotide sequence selected from the group consisting of (5'→3'):
 - (i) usGfsusUfaAfaCfaUfgCfcUfaAfaCfgyusu (SEQ ID NO: 913);
 - (ii) usGfsusUfaAfaCfaUfgCfcUfaAfaCfgyusu (SEQ ID NO: 958);
 - (iii) usGfsuUfaAfaCfaUfgCfcUfaAfaCfgyCfsg (SEQ ID NO: 959); and (iv) usGfsuUfaAfacaugCfcUfaAfaCfgyCfsu (SEQ ID NO: 960);

wherein, a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s is a phosphorothioate linkage; and

- (b) a sense strand that is at least substantially complementary to the antisense strand, wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides; and

wherein the sense strand is linked to a targeting group that comprises N-acetyl-galactosamine.

2. The RNAi agent of claim 1, wherein the sense strand is no more than 30 nucleotides in length, and the antisense strand is no more than 30 nucleotides in length.

3. The RNAi agent of claim 2, wherein the sense strand is no more than 24 nucleotides in length, and the antisense strand is no more than 24 nucleotides in length.

4. The RNAi agent of claim 3, wherein the sense strand and the antisense strand are each between 21 and 24 nucleotides in length.

5. The RNAi agent of claim 4, wherein the sense strand and the antisense strand are each 21 nucleotides in length.

6. The RNAi agent of claim 1, wherein the RNAi agent has two blunt ends.

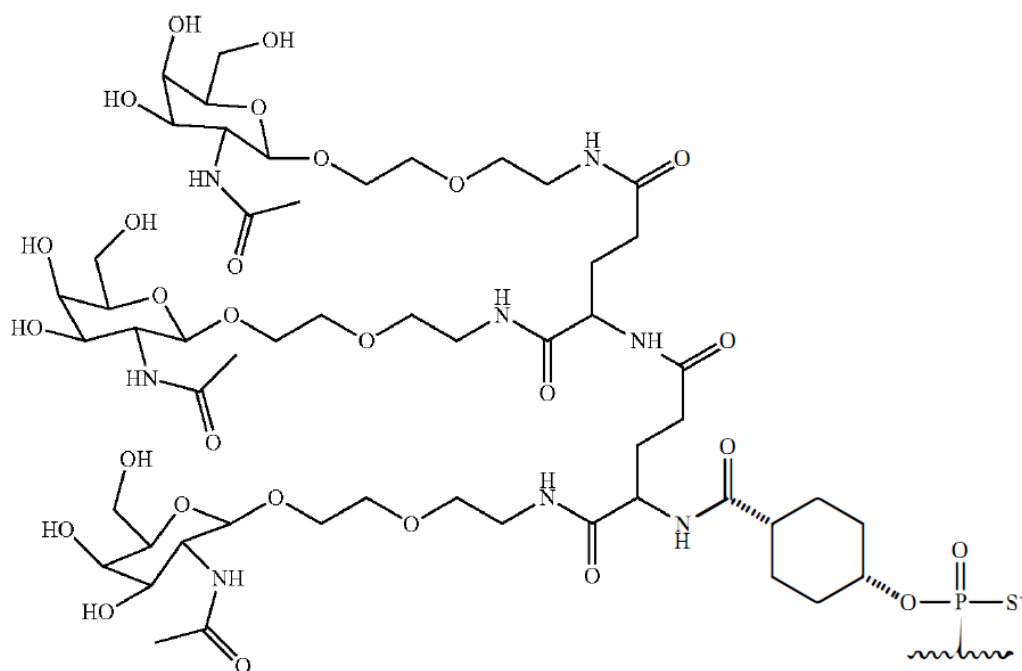
7. The RNAi agent of claim 1, wherein the targeting group comprises an N-acetyl-galactosamine trimer.

8. The RNAi agent of claim 1, wherein the targeting group has a structure selected from the group consisting of: (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), (NAG39)s.

9. The RNAi agent of claim 7, wherein the RNAi agent comprises a targeting group that is conjugated to the 5' terminal end of the sense strand.

10. The RNAi agent of claim 1, wherein the sense strand comprises the sequence (5'→3') agcguuuuGfGfCfauguuuuaca (SEQ ID NO: 1279), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; and wherein optionally present on the sense strand is one or two inverted abasic deoxyribose residues (invAb) and/or one, two, three, or four phosphorothioate internucleoside linkages.

11. The RNAi agent of claim 10, wherein the sense strand comprises the sequence (5'→3') (NAG37)s(invAb)sagcguuuuGfGfCfauguuuuacac(invAb) (SEQ ID NO: 1033), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; (invAb) is an inverted abasic deoxyribose residue, and (NAG37)s has the following chemical structure:

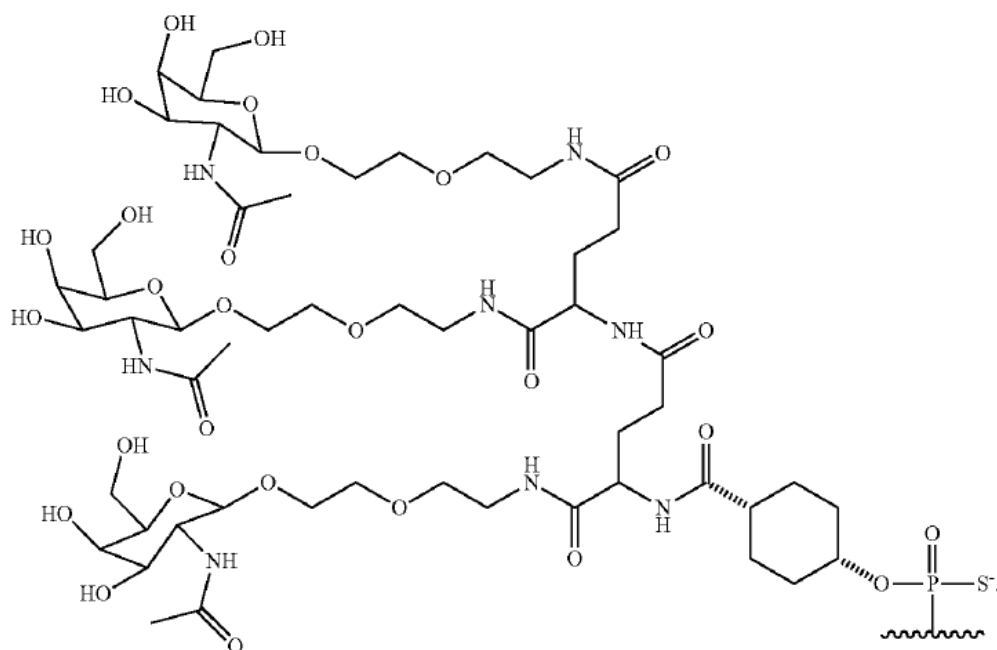


12. The RNAi agent of claim 11, wherein the RNAi agent has the duplex structure of AD04837 (SEQ ID NOs: 960 and 1033).

13. The RNAi agent of claim 1, wherein the sense strand comprises the sequence (5'→3') cguuuuGfGfCfauguuuuacausu (SEQ ID NO: 1276), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; and wherein optionally present on the sense strand is one or two inverted abasic deoxyribose residues (invAb) and/or one, two, three, or four phosphorothioate internucleoside linkages.

14. The RNAi agent of claim 13, wherein the sense strand comprises the sequence (5'→3') (NAG37)s(invAb)scguuuuGfGfCfauguuuuacausu(invAb) (SEQ ID NO: 1028), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; (invAb) is an inverted abasic deoxyribose

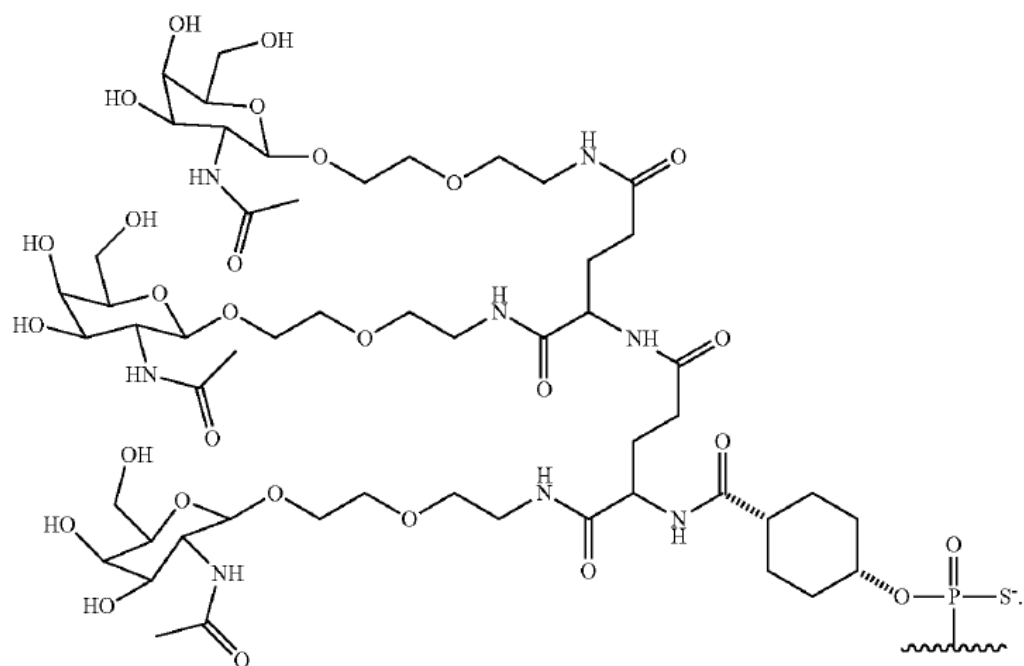
residue, and (NAG37)s has the following chemical structure:



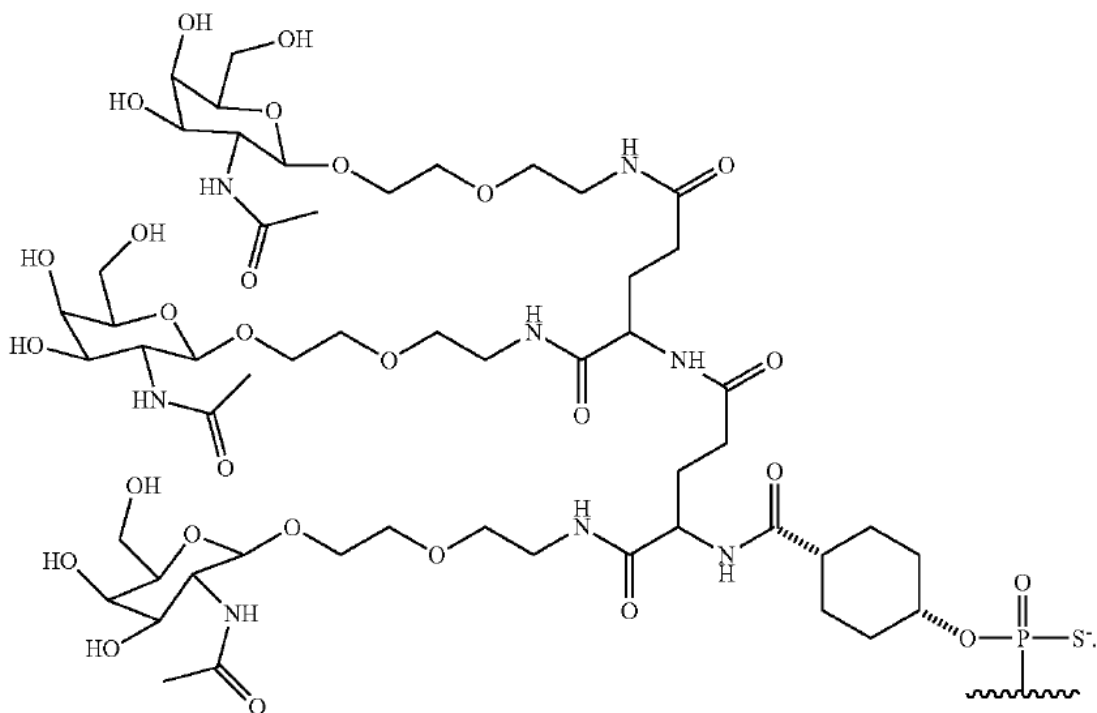
15. The RNAi agent of claim 14, wherein the RNAi agent has the duplex structure of AD04828 (SEQ ID NOs: 913 and 1028).

16. The RNAi agent of claim 1, wherein the sense strand comprises the sequence (5'→3') gcguuuuGfGfCfauguuuuacausu (SEQ ID NO: 1277), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; and wherein optionally present on the sense strand is one or two inverted abasic deoxyribose residues (invAb) and/or one, two, three, or four phosphorothioate internucleoside linkages.

17. The RNAi agent of claim 1, wherein the sense strand comprises the sequence (5'→3') (NAG37)s(invAb)sgcguuuuGfGfCfauguuuuacausu(invAb) (SEQ ID NO: 1030), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; (invAb) is an inverted abasic deoxyribose residue, and (NAG37)s has the following chemical structure:



18. The RNAi agent of claim 17, wherein the RNAi agent has the duplex structure of AD04831 (SEQ ID NOs: 958 and 1030).
19. The RNAi agent of claim 1, wherein the sense strand comprises the sequence (5'→3') cgcguaaGfGfCfauguuaaca (SEQ ID NO: 1278), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; and wherein optionally present on the sense strand is one or two inverted abasic deoxyribose residues (invAb) and/or one, two, three, or four phosphorothioate internucleoside linkages.
20. The RNAi agent of claim 19, wherein the sense strand comprises the sequence (5'→3') (NAG37)s(invAb)scgcuuaGfGfCfauguuaacas(invAb) (SEQ ID NO: 1024), wherein a, c, g, and u are 2'-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf are 2'-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s is a phosphorothioate linkage; (invAb) is an inverted abasic deoxyribose residue, and (NAG37)s has the following chemical structure:



21. The RNAi agent of claim 20, wherein the RNAi agent has the duplex structure of AD04836 (SEQ ID NOs: 959 and 1024).
22. A composition comprising the RNAi agent of claim 1, and at least one pharmaceutically acceptable excipient.
23. The composition of claim 22, wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringes, or vials.
24. The composition of claim 22, wherein the composition is formulated for administration by subcutaneous injection.
25. Use of a composition of claim 22 in the manufacture of a medicament for inhibiting the expression of an AAT gene in a subject.
26. Use of a composition of claim 22 in the manufacture of a medicament for the treatment of alpha-1 antitrypsin deficiency (AATD) in a subject.
27. Use of a composition of claim 22 in the manufacture of a medicament for the treatment of a condition or disease caused by alpha-1 antitrypsin deficiency (AATD) in a subject.
28. A composition comprising the RNAi agent of claim 12, and at least one pharmaceutically acceptable excipient.

29. A composition comprising the RNAi agent of claim 15, and at least one pharmaceutically acceptable excipient.
30. A composition comprising the RNAi agent of claim 18, and at least one pharmaceutically acceptable excipient.
31. A composition comprising the RNAi agent of claim 20, and at least one pharmaceutically acceptable excipient.
32. The RNAi agent of claim 1, wherein the RNAi agent has the duplex structure of SEQ ID NOs: 960 and 1279.
33. The RNAi agent of claim 1, wherein the RNAi agent has the duplex structure of sequence pairs SEQ ID NOs: 913 and 1276.
34. The RNAi agent of claim 1, wherein the RNAi agent has the duplex structure of sequence pairs SEQ ID NOs: 958 and 1277.
35. The RNAi agent of claim 1, wherein the RNAi agent has the duplex structure of sequence pairs SEQ ID NOs: 959 and 1278.
36. Use of a composition of claim 28 in the manufacture of a medicament for the treatment of alpha-1 antitrypsin deficiency (AATD), including the treatment of a condition or disease caused by or attributable to AATD.
37. Use of a composition of claim 29 in the manufacture of a medicament for the treatment of alpha-1 antitrypsin deficiency (AATD), including the treatment of a condition or disease caused by or attributable to AATD.
38. Use of a composition of claim 30 in the manufacture of a medicament for the treatment of alpha-1 antitrypsin deficiency (AATD), including the treatment of a condition or disease caused by or attributable to AATD.
39. Use of a composition of claim 31 in the manufacture of a medicament for the treatment of alpha-1 antitrypsin deficiency (AATD), including the treatment of a condition or disease caused by or attributable to AATD.