

Claims:

1. An RNAi agent for inhibiting expression of a Mucin 5AC gene, comprising:
an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2 or Table 3; 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 all or substantially all of the nucleotides are modified nucleotides.
3. The RNAi agent of claim 2, wherein the modified nucleotides are 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.
4. The RNAi agent of any one of claims 1-3, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3 or Table 11.
5. The RNAi agent of any one of claims 1-4, wherein the sense strand comprises the nucleotide sequence of any one of the modified sense strand sequences provided in Table 4 or Table 11.
6. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3 or Table 11, and the sense strand comprises the nucleotide sequence of any one of the modified sense strand sequences provided in Table 4 or Table 11.
7. The RNAi agent of any one of claims 1-6, wherein the sense strand is between 18 and 30 nucleotides in length, and the antisense strand is between 18 and 30 nucleotides in length.
8. The RNAi agent of claim 7, wherein the sense strand and the antisense strand are each 21 nucleotides in length.
9. The RNAi agent of claim 8, wherein the RNAi agent has two blunt ends.

10. The RNAi agent of any one of claims 1-9, wherein the sense strand comprises one or two terminal caps.
11. The RNAi agent of any one of claims 1-10, wherein the sense strand comprises one or two inverted abasic residues.
12. The RNAi agent of claim 1, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex having the structure of any one of the duplexes in Table 8A, Table 8B, Table 8C, Table 9, Table 10A, or Table 10B.
13. The RNAi agent of claim 1, wherein the antisense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); or

UUCUUGUUCAGGCAAUCA (SEQ ID NO:83).
14. The RNAi agent of claim 1, wherein the antisense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525); or

UUCUUGUUCAGGCAAUCAGC (SEQ ID NO:1535).
15. The RNAi agent of claim 1, wherein the sense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UGUUCUGCGACUACUACAA (SEQ ID NO:568); or

UGAUUUGCCUGAACAAAGAA (SEQ ID NO:572).
16. The RNAi agent of claim 13, 14, or 15, wherein all or substantially all of the nucleotides are modified nucleotides.
17. The RNAi agent of claim 1, wherein the antisense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127);

usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1065);

usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166); or

cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191);

wherein a, c, g, and u represent 2'-O-methyl adenosine, 2'-O-methyl cytidine, 2'-O-methyl guanosine, and 2'-O-methyl uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, 2'-fluoro cytidine, 2'-fluoro guanosine, and 2'-fluoro uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyl uridine; s represents a phosphorothioate linkage; and wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides.

18. 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 following nucleotide sequences (5' → 3'):

gscuguucuGfCfGfacuacuacaa (SEQ ID NO:1265); or

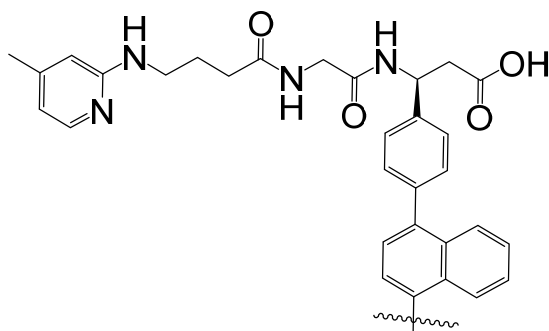
gscugauUfuGfcCfugaacaagaa (SEQ ID NO:1315);

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

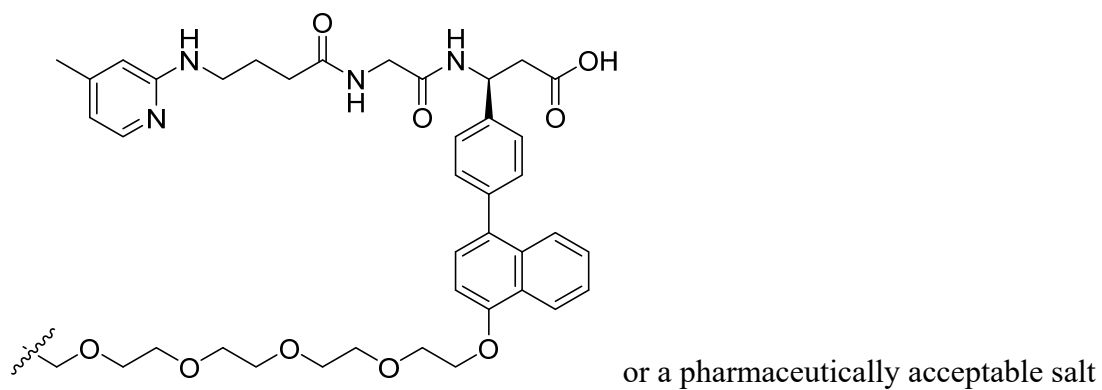
19. The RNAi agent of any one of claims 14-18, wherein the sense strand further includes inverted abasic residues at the 3' terminal end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both.

20. The RNAi agent of any one of claims 1-19, wherein the RNAi agent is linked to a targeting ligand.

21. The RNAi agent of claim 20, wherein the targeting ligand comprises the structure:

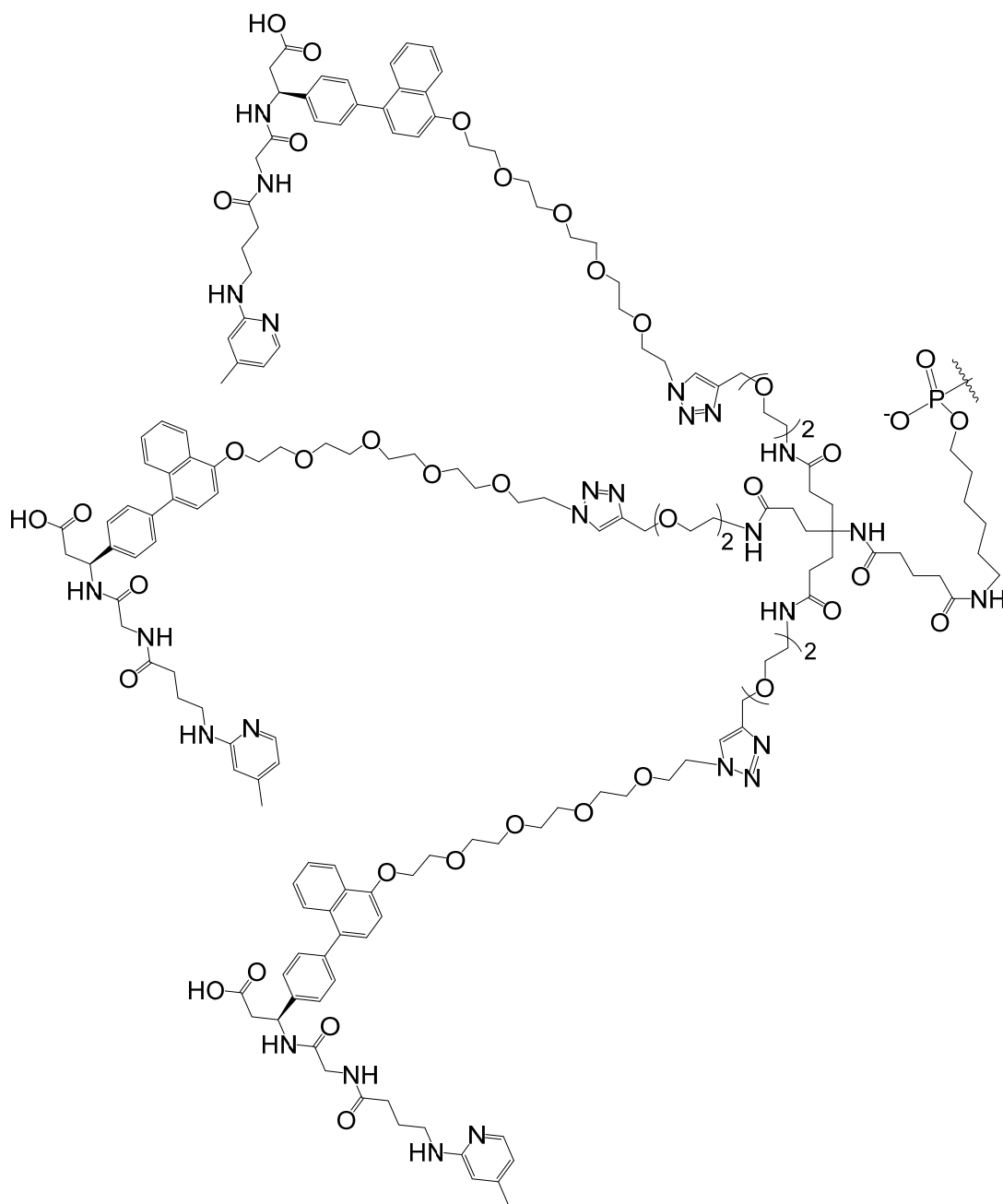


or a pharmaceutically acceptable salt thereof, or



thereof, wherein  indicates the point of connection to the RNAi agent.

22. The RNAi agent of any one of claims 20-21, wherein RNAi agent is conjugated to a targeting ligand having the following structure:



, or a

pharmaceutically acceptable salt thereof, wherein  indicates the point of connection to the RNAi agent.

23. The RNAi agent of any one of claims 20-22, wherein the targeting ligand is conjugated to the 5' terminal end of the sense strand.
24. A composition comprising the RNAi agent of any one of claims 1-23, wherein the composition further comprises a pharmaceutically acceptable excipient.

25. The composition of claim 24, further comprising a second RNAi agent capable of inhibiting the expression of Mucin 5AC gene expression.
26. The composition of any one of claims 24-25, further comprising one or more additional therapeutics.
27. The composition of any one of claims 24-26, wherein the composition is formulated for administration by inhalation.
28. The composition of claim 27, wherein the composition is delivered by a metered-dose inhaler, jet nebulizer, vibrating mesh nebulizer, or soft mist inhaler.
29. The composition of any of claims 24-28, wherein the RNAi agent is a sodium salt.
30. The composition according to any one of claims 24-29, for use in the treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC gene expression.
31. Use of the composition according to any one of claims 24-29 in the preparation of a medicament for treating a disease, disorder, or a symptom that is mediated at least in part by Mucin 5AC gene expression.
32. The composition of claim 30 or the use of claim 31, wherein the disease is asthma.
33. The composition of claim 30 or the use of claim 31, wherein the disease is severe asthma.