

Claims

1. An RNAi agent for inhibiting expression of a matrix metalloproteinase 7 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 all or substantially all of the nucleotides are modified with 2'-O-methyl nucleotides, 2'-fluoro nucleotides, or combinations thereof.
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 sequences provided in Table 3.
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 sequences provided in Table 4.
6. The RNAi agent of any one of claims 1-5, wherein the sense strand comprises one or two inverted abasic residues.
7. 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 7A, Table 7B, Table 8, Table 9, or Table 10.
8. The RNAi agent of claim 1, comprising an antisense strand that 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'):
AGACAUUCAAAAACCAACU (SEQ ID NO:175);
UUGACACUAAUCGAUCCAC (SEQ ID NO:123);
UGACAUUCAAAAACCAACU (SEQ ID NO:176);
AGACAUUCAAAAACCAACUGC (SEQ ID NO:674);
UUGACACUAAUCGAUCCACUG (SEQ ID NO:661); or
UGACAUUCAAAAACCAACUGC (SEQ ID NO:679).

9. The RNAi agent of claim 8, 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'):

AGUUGGUUUUUGAAUGUCU (SEQ ID NO:325);
GUGGAUCGAUUAGUGUCAA (SEQ ID NO:273);
AGUUGGUUUUUGAAUGUCA (SEQ ID NO:326);
GCAGUUGGUUUUUGAAUGUCU (SEQ ID NO:720);
CAGUGGAUCGAUUAGUGUCAA (SEQ ID NO:724); or
GCAGUUGGUUUUUGAAUGUCA (SEQ ID NO:726).

10. The RNAi agent of claim 8 or 9, wherein all or substantially all of the nucleotides are modified nucleotides.

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

asGfsascauucAfaaAfaCfcAfacugsc (SEQ ID NO:396);
usUfsgsacacUfaAfuCfGafuCfcacusg (SEQ ID NO:393); or
cPrpuGfacauucAfaaAfaCfcAfacugsc (SEQ ID NO:406);

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.

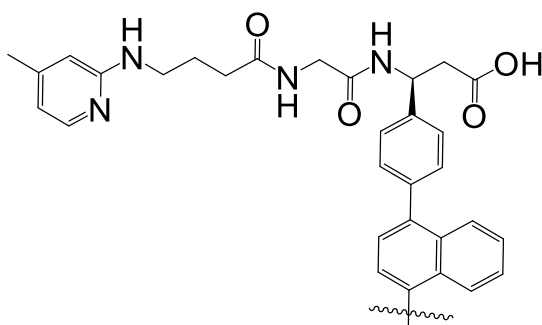
12. The RNAi agent of claim 1, wherein the sense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

gscaguuggUfuUfuUfgaaugucu (SEQ ID NO:522);
csaguggauCfGafuUfagugucua (SEQ ID NO:524);

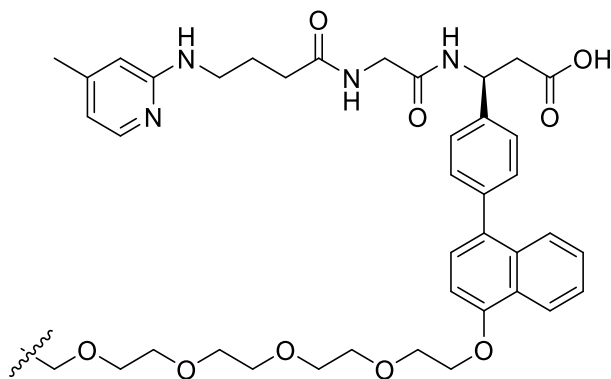
gscaguuggUfuUfuUfgaauca (SEQ ID NO:526);

wherein a, c, g, i, and u represent 2'-O-methyl adenosine, 2'-O-methyl cytidine, 2'-O-methyl guanosine, 2'-O-methyl inosine, 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.

13. The RNAi agent of any one of claims 8-12, 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.
14. The RNAi agent of any one of claims 1-13, wherein the RNAi agent is linked to a targeting ligand.
15. The RNAi agent of claim 14, wherein the targeting ligand comprises the structure:



or a pharmaceutically acceptable salt thereof, or



or a pharmaceutically acceptable salt

thereof,

wherein  indicates the point of connection to the RNAi agent.

- [illegible]

17. The RNAi agent of any one of claims 14-16, wherein the targeting ligand is conjugated to the 5' terminal end of the sense strand.
18. A composition comprising the RNAi agent of any one of claims 1-17, wherein the composition further comprises a pharmaceutically acceptable excipient.
19. The composition of claim 18, wherein the RNAi agent is a sodium salt.
20. The composition of claim 18, wherein the pharmaceutically acceptable excipient is a buffered saline solution.
21. A RNAi agent of any one of claims 1-17 or the composition of any one of claims 18-20, for use in inhibiting expression of a MMP7 gene in a cell.
22. The composition of any one of claims 18-20, for use in a method of treating one or more symptoms or diseases associated with enhanced or elevated membrane MMP7 activity levels.
23. The composition of claim 22, wherein the disease is idiopathic pulmonary fibrosis (IPF), asthma, another type of fibrosis, chronic inflammation, interstitial lung diseases (ILD), SARS-COV-2 or another type of infectious disease, acute respiratory distress syndrome (ARDS) or another type of acute lung injury, pulmonary hypertension, cancer, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), fatty liver disease, biliary atresia, and chronic kidney disease (CKD).
24. The composition of claim 23, wherein the disease is idiopathic pulmonary fibrosis (IPF).
25. Use of the composition according to any one of claims 18-20, for the manufacture of a medicament for treatment of a disease, disorder, or symptom that is mediated at least in part by matrix metalloproteinase 7 and/or matrix metalloproteinase 7 gene expression.
26. The use of claim 25, wherein the disease is pulmonary inflammation.