CLAIMS

1. An RNAi agent for inhibiting expression of an alpha-ENaC gene, comprising:
an antisense strand comprising the nucleotide sequence (5′ → 3′) UAUUUGUUCUGGUUGCACAGG (SEQ ID NO:3); and
a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand;
wherein all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides.

2. The RNAi agent of claim 1, wherein the antisense strand, the sense strand, or both the antisense and sense strands includes at least one modified internucleoside linkage.

3. The RNAi agent of claim 1, wherein the modified nucleotides are each independently selected from the group consisting of: 2′-O-methyl nucleotides, 2′-fluoro nucleotides, 2′-deoxy nucleotides, 2′,3′-seco nucleotide mimics, locked nucleotides, 2'-F-arabino nucleotides, 2′-methoxyethyl nucleotides, abasic nucleotides, ribitols, inverted nucleotides, inverted 2′-O-methyl nucleotides, inverted 2′-deoxy nucleotides, 2′-amino-modified nucleotides, 2′-alkyl-modified nucleotides, morpholino nucleotides, vinyl phosphonate containing nucleotides, cyclopropyl phosphonate containing nucleotides, and 3′-O-methyl nucleotides.

4. The RNAi agent of claim 1, wherein all or substantially all of the nucleotides are modified with 2′-O-methyl nucleotides, 2′-fluoro nucleotides, or combinations thereof.

5. The RNAi agent of claim 1, wherein the sense strand comprises the nucleotide sequence of (5′ → 3′) CCUGUGCAACCAGAACAAAUA (SEQ ID NO:5).

6. The RNAi agent of claim 1, wherein the RNAi agent is linked to a targeting ligand.

7. The RNAi agent of claim 5, wherein the RNAi agent is linked to a targeting ligand.

8. The RNAi agent of claim 6, wherein the targeting ligand comprises an integrin targeting ligand.

9. The RNAi agent of claim 8, wherein the integrin targeting ligand is an αvβ6 integrin targeting ligand.

10. The RNAi agent of claim 9, wherein the targeting ligand is conjugated to the sense strand.

11. The RNAi agent of claim 10, wherein the targeting ligand is conjugated to the 5' terminal end of the sense strand.

12. The RNAi agent of claim 10, wherein the sense strand and the antisense strand are each between 18 and 27 nucleotides in length.

13. The RNAi agent of claim 12, wherein the sense strand and the antisense strand are each between 18 and 24 nucleotides in length.

14. The RNAi agent of claim 13, wherein the sense strand and the antisense strand are each 21 nucleotides in length.

15. The RNAi agent of claim 10, wherein the RNAi agent has two blunt ends.

16. The RNAi agent of claims 10, wherein the sense strand comprises a terminal cap.

17. The RNAi agent of claim 16, wherein the sense strand comprises one or two inverted abasic residues.

18. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence (5′ → 3′):

usAfsusUfuGfuUfcUfgGfuUfgCfaCfaGfsg (SEQ ID NO:2); or

cPrpusAfsusUfuGfuUfcUfgGfuUfgCfaCfaGfsg (SEQ ID NO:10);

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s represents a phosphorothioate linkage, and cPrpu represents a 5'-cyclopropyl phosphonate-2′-O-methyl uridine.

19. The RNAi agent of claim 18, wherein the sense strand comprises the nucleotide sequence (5′ → 3′):

cscugugcaAfCfCfagaacaaaua (SEQ ID NO:4);

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage.

20. The RNAi agent of claim 19, wherein the sense strand of the RNAi agent is linked to targeting ligand.

21. The RNAi agent of claim 20, wherein the targeting ligand has affinity for a cell receptor expressed on an epithelial cell.

22. The RNAi agent of claims 20, wherein the targeting ligand is an αvβ6 integrin targeting ligand.

23. A composition comprising the RNAi agent of claim 19, wherein the composition comprises a pharmaceutically acceptable excipient.

24. The composition of claim 23, further comprising a second RNAi agent for inhibiting the expression of alpha-ENaC.

25. The composition of claim 23, further comprising one or more additional therapeutics.

26. The composition of claim 23, wherein the composition is formulated for administration by inhalation.

27. The composition of claim 26, wherein the composition is to be delivered by a metered-dose inhaler, jet nebulizer, vibrating mesh nebulizer, or soft mist inhaler.

28. A method for inhibiting expression of an alpha-ENaC gene in an isolated cell, the method comprising introducing into a cell an effective amount of an RNAi agent of claim 1.

29. A method for inhibiting expression of an alpha-ENaC gene in an isolated cell, the method comprising introducing into a cell an effective amount of the composition of claim 23.

30. The method of claim 28 or claim 29, wherein the alpha-ENaC gene expression is inhibited by at least about 30%.

31. The RNAi agent of claim 19, wherein the sense strand further includes an inverted abasic residue at the 3’ terminal end.

32. The RNAi agent of claim 31, wherein the sense strand comprises the nucleotide sequence cscugugcaAfCfCfagaacaaauas(invAb) (SEQ ID NO:178), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s represents a phosphorothioate linkage; and (invAb) represents an inverted abasic residue.

33. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence (5′ → 3′) usAfsusUfuGfuUfcUfgGfuUfgCfaCfaGfsg (SEQ ID NO:2), and the sense strand comprises the nucleotide sequence (5′ → 3′) cscugugcaAfCfCfagaacaaauas(invAb) (SEQ ID NO:178),
wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s represents a phosphorothioate linkage; and (invAb) represents an inverted abasic residue.

34. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence (5′ → 3′) cPrpusAfsusUfuGfuUfcUfgGfuUfgCfaCfaGfsg (SEQ ID NO:10), and the sense strand comprises the nucleotide sequence (5′ → 3′) cscugugcaAfCfCfagaacaaauas(invAb) (SEQ ID NO:178),
wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; s represents a phosphorothioate linkage; and cPrpu represents a 5’-cyclopropyl phosphonate-2′-O-methyl uridine.

35. The RNAi agent of any one of claims 32-34, wherein the sense strand and the antisense strand are each 21 nucleotides in length.

36. The RNAi agent of claim 33 or claim 34, wherein the sense strand of the RNAi agent is linked to an αvβ6 integrin targeting ligand.