

CLAIMS

What is claimed is:

1. A composition comprising an oligonucleotide that targets *MST1* and wherein the composition improves:

- (a) a lung function measurement;
- (b) a leukocyte measurement;
- (c) a chronic obstructive pulmonary disease (COPD) symptom or exacerbation measurement; or
- (d) an asthma symptom or exacerbation measurement.

2. The composition of claim 1, wherein the lung function measurement comprises a forced expiratory volume in 1 second (FEV1) measurement, a forced expiratory volume in 1 second percent predicted (FEV1pp) measurement, a forced vital capacity (FVC) measurement, a FEV1/FVC ratio measurement, a forced expiratory volume, or a peak expiratory flow measurement.

3. The composition of claim 1, wherein the oligonucleotide comprises a modified internucleoside linkage.

4. The composition of claim 3, wherein the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof.

5. The composition of claim 1, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages.

6. The composition of claim 1, wherein the oligonucleotide comprises a modified nucleoside.

7. The composition of claim 6, wherein the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HNA), cyclohexene nucleic acid (CeNA), 2'-O-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof.

8. The composition of claim 1, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 modified nucleosides.

9. The composition of claim 1, wherein the oligonucleotide comprises a lipid, a sugar moiety, or an integrin targeting ligand attached at a 3' or 5' terminus of the oligonucleotide.

10. The composition of claim 9, wherein the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α -tocopherol, or a combination thereof.

11. The composition of claim 9, wherein the sugar comprises N-acetylgalactosamine (GalNAc), N-acetylglucosamine (GlcNAc), or mannose.

12. The composition of claim 9, wherein the integrin comprises integrin alpha-v-beta-6, or the integrin targeting ligand comprises an arginine-glycine-aspartic acid (RGD) peptide.

13. The composition of claim 1, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, and each strand is independently 12-30 nucleosides in length.

14. A composition comprising an oligonucleotide that inhibits the expression of *MST1*, wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 6185; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 6185.

15. The composition of claim 14, wherein any one of the following is true with regard to the sense strand:

all purines comprise 2'-fluoro modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-fluoro modified purines, and all pyrimidines comprise 2'-O-methyl modified pyrimidines;

all pyrimidines comprise 2'-fluoro modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines;

all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines; or

all pyrimidines comprise 2'-fluoro modified pyrimidines, and all purines comprise 2'-O-methyl modified purines.

16. The composition of claim 14, wherein any one of the following is true with regard to the antisense strand:

all purines comprise 2'-fluoro modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise 2'-fluoro modified pyrimidines;

all pyrimidines comprise 2'-fluoro modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines;

all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines; or

all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise 2'-fluoro modified purines.

17. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

18. Use of a composition comprising an oligonucleotide that modulates the expression of MST1 in the manufacture of a medicament for treating a subject having a lung disorder, wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 6185; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 6185.

19. The use of claim 18, wherein the lung disorder comprises COPD, acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), bronchiectasis, cough, dyspnea, mucus hypersecretion, lung cancer, interstitial lung disease, or pulmonary fibrosis.

20. The composition of claim 1, wherein the leukocyte measurement comprises a neutrophil measurement, an eosinophil measurement, a basophil measurement, a monocyte measurement, a lymphocyte measurement, a macrophage measurement, a neutrophil lymphocyte ratio measurement, or a combination thereof.

21. A composition comprising an oligonucleotide that modulates the expression of MST1 for use in therapy, wherein the oligonucleotide comprises:

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 6185; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 6185.