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(54) Title: TREATMENT OF MST1R RELATED DISEASES AND DISORDERS

(57) Abstract: Disclosed herein are compositions comprising an oligonucleotide that targets *MST1R*. The oligonucleotide may include a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO). Also provided herein are methods of treating conditions associated with *MST1R* mutations that include providing an oligonucleotide that targets *MST1R* to a subject.

TREATMENT OF MST1R RELATED DISEASES AND DISORDERS**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/211,370, filed June 16, 2021, which application is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 2, 2022, is named 54462-731_601_SL.txt and is 2,357,478 bytes in size.

BACKGROUND

[0003] Lung disorders are a common problem, and may affect a wide variety of persons. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0004] Described herein are compositions comprising an oligonucleotide that targets *MST1R*. Described herein are compositions comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount reduces a *MST1R* mRNA level or *MST1R* protein level. Described herein are compositions comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount increases a lung function measurement. In some embodiments, 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. In some embodiments, the lung function measurement is increased by about 10% or more, as compared to prior to administration. Described herein are compositions comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases a leukocyte measurement. In some embodiments, the leukocyte measurement comprises a lung leukocyte measurement. In some embodiments, the leukocyte measurement comprises a circulating leukocyte measurement. In some embodiments, the leukocyte measurement comprises a neutrophil measurement, eosinophil measurement, basophil measurement, monocyte measurement, or lymphocyte measurement, or a combination thereof. In some embodiments, the leukocyte measurement is decreased by about 10% or more, as compared to prior to administration. Described herein are compositions comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases a chronic obstructive pulmonary disease (COPD) or asthma exacerbation measurement. In some embodiments, the COPD or asthma exacerbation measurement is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a

combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. In some embodiments, 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. In some embodiments, the oligonucleotide comprises a modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises a 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. In some embodiments, the modified nucleoside comprises one or more 2' fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. In some embodiments, 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. In some embodiments, the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosaheptaenoyl, myristyl, palmityl stearyl, or α -tocopherol, or a combination thereof. In some embodiments, the oligonucleotide comprises a sugar moiety attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the oligonucleotide comprises an integrin targeting ligand attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the integrin comprises integrin α -v- β -6. In some embodiments, the integrin targeting ligand comprises an arginine-glycine-aspartic acid (RGD) peptide. In some embodiments, the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand. In some embodiments, the sense strand is 12-30 nucleosides in length. In some embodiments, the antisense strand is 12-30 nucleosides in length. Described herein are compositions comprising an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 9818. In some embodiments, 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' methyl modified pyrimidines; all purines comprise 2' methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines; all purines comprise 2' fluoro modified purines, and all pyrimidines comprise 2' methyl modified pyrimidines; all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines; all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines; or all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise 2' methyl modified purines. In some embodiments, the sense strand comprises any one of modification patterns 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S. In some embodiments,

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' methyl modified pyrimidines; all purines comprise 2' methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines; all purines comprise 2' 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' methyl modified purines; all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines; or all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise 2' fluoro modified purines. In some embodiments, the antisense strand comprises any one of modification patterns 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 1-4754, and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 4755-9508. In some embodiments, the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. Described herein are compositions comprising an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and a nucleoside sequence complementary to about 12-30 contiguous nucleosides of SEQ ID NO: 9818. Some embodiments include a pharmaceutically acceptable carrier. Described herein are methods of treating a subject having a lung disorder, comprising administering an effective amount of the composition to the subject. In some embodiments, the lung disorder COPD, acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), cough, lung cancer, interstitial lung disease, or pulmonary fibrosis.

DETAILED DESCRIPTION

[0005] Large-scale human genetic data can improve the success rate of pharmaceutical discovery and development. A Genome Wide Association Study (GWAS) may detect associations between genetic variants and traits in a population sample. A GWAS may enable better understanding of the biology of disease, and provide applicable treatments. A GWAS can utilize genotyping and/or sequencing data, and often involves an evaluation of millions of genetic variants that are relatively evenly distributed across the genome. The most common GWAS design is the case-control study, which involves comparing variant frequencies in cases versus controls. If a variant has a significantly different frequency in cases versus controls, that variant is said to be associated with disease. Association statistics that may be used in a GWAS are p-values, as a measure of statistical significance; odds ratios (OR), as a measure of effect size; or beta coefficients (beta), as a measure of effect size. Researchers often assume an additive genetic model and calculate an allelic odds ratio, which is the increased (or decreased) risk of disease conferred by each additional copy of an allele (compared to carrying no copies of that allele). An additional concept in design and interpretation of GWAS is that of linkage disequilibrium, which is the non-random association of alleles. The presence of linkage disequilibrium can obfuscate which variant is “causal.”

[0006] Functional annotation of variants and/or wet lab experimentation can identify the causal genetic variant identified via GWAS, and in many cases may lead to the identification of disease-causing genes.

In particular, understanding the functional effect of a causal genetic variant (for example, loss of protein function, gain of protein function, increase in gene expression, or decrease in gene expression) may allow that variant to be used as a proxy for therapeutic modulation of the target gene, or to gain insight into potential therapeutic efficacy and safety of a therapeutic that modulates that target.

[0007] Identification of such gene-disease associations has provided insights into disease biology and may be used to identify novel therapeutic targets for the pharmaceutical industry. In order to translate the therapeutic insights derived from human genetics, disease biology in patients may be exogenously ‘programmed’ into replicating the observation from human genetics. There are several potential options for therapeutic modalities that may be brought to bear in translating therapeutic targets identified via human genetics into novel medicines. These may include well established therapeutic modalities such as small molecules and monoclonal antibodies, maturing modalities such as oligonucleotides, and emerging modalities such as gene therapy and gene editing. The choice of therapeutic modality can depend on several factors including the location of a target (for example, intracellular, extracellular, or secreted), a relevant tissue (for example, lung) and a relevant indication.

[0008] The *MST1R* (*macrophage-stimulating 1 receptor*) gene is located on chromosome 3, and encodes macrophage-stimulating 1 receptor (MST1R), also known as macrophage-stimulating protein receptor or Recepteur d'Origine Nantais (RON) kinase. The *MST1R* gene may encode various transcripts or splice variants. MST1R may include 1400 amino acids and have a mass of about 152 kDa. MST1R may be cleaved into an alpha and beta chain. MST1R may comprise a receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding macrophage-stimulating protein (MSP) encoded by *MST1* (*macrophage-stimulating 1*). MSP may also be referred to as MST1 protein. MST1R may be intracellular. MST1R may be cell membrane-bound. *MST1R* may be expressed in lungs. MST1R may bind or interact with MSP and stimulate lung ciliary motility. The MSP may be secreted by the liver and enter the bloodstream prior to interacting with MST1R at the lung. An example of an MST1R amino acid sequence, and further description of MST1R is included at uniprot.org under accession no. Q04912 (last modified March 28, 2018).

[0009] Here, it is shown that a genetic variant that may result in loss of function of the *MST1R* gene in humans are associated with decreased risk of chronic obstructive pulmonary disease (COPD), family history of COPD, asthma, and use of inhaled beta agonist medication. Also shown is that genetic variants that may result in loss of function of the gene encoding MST1R's binding partner, MST1, are also associated with decreased risk of COPD, family history of COPD, asthma, and use of inhaled beta agonist medication. Therefore, inhibition of MST1R may serve as a therapeutic strategy for treatment of a lung disorder such as COPD, acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), cough, lung cancer, interstitial lung disease, or pulmonary fibrosis.

[0010] Disclosed herein, are methods or compositions that inhibit or target *MST1R*. Where inhibition or targeting of *MST1R* is disclosed, it is contemplated that some embodiments may include inhibiting or targeting a MST1R protein or *MST1R* RNA. For example, by inhibiting or targeting an RNA (e.g. mRNA)

encoded by the *MST1R* gene using an oligonucleotide described herein, the MST1R protein may be inhibited or targeted as a result of there being less production of the MST1R protein by translation of the *MST1R* RNA; or a MST1R protein may be targeted or inhibited by an oligonucleotide that binds or interacts with a *MST1R* RNA and reduces production of the MST1R protein from the *MST1R* RNA. Thus, targeting *MST1R* may refer to binding a *MST1R* RNA and reducing *MST1R* RNA or MST1R protein levels. The oligonucleotide may include a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO). Also provided herein are methods of treating a lung disorder by providing an oligonucleotide that targets *MST1R* to a subject in need thereof.

I. COMPOSITIONS

[0011] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide. In some embodiments, the composition comprises an oligonucleotide that targets *MST1R*. In some embodiments, the composition consists of an oligonucleotide that targets *MST1R*. In some embodiments, the oligonucleotide reduces *MST1R* mRNA expression in the subject. In some embodiments, the oligonucleotide reduces MST1R protein expression in the subject. The oligonucleotide may include a small interfering RNA (siRNA) described herein. The oligonucleotide may include an antisense oligonucleotide (ASO) described herein. In some embodiments, a composition described herein is used in a method of treating a disorder in a subject in need thereof. Some embodiments relate to a composition comprising an oligonucleotide for use in a method of treating a disorder as described herein. Some embodiments relate to use of a composition comprising an oligonucleotide, in a method of treating a disorder as described herein.

[0012] Some embodiments include a composition comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases *MST1R* mRNA or MST1R protein levels in a cell, fluid or tissue. In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases *MST1R* mRNA levels in a cell or tissue. In some embodiments, the cell is a lung cell, lung epithelial cell, type I or II alveolar cell, macrophage, alveolar macrophage, goblet cell, club cell, or fibroblast. In some embodiments, the tissue is lung tissue. In some embodiments, the *MST1R* mRNA levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the *MST1R* mRNA levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the *MST1R* mRNA levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the *MST1R* mRNA levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the *MST1R* mRNA levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the *MST1R* mRNA levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the

MST1R mRNA levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0013] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases *MST1R* protein levels in a cell or tissue. In some embodiments, the cell is a lung cell, lung epithelial cell, type I or II alveolar cell, macrophage, alveolar macrophage, goblet cell, club cell, or fibroblast. In some embodiments, the tissue is lung tissue. In some embodiments, the *MST1R* protein levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the *MST1R* protein levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the *MST1R* protein levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the *MST1R* protein levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the *MST1R* protein levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the *MST1R* protein levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the *MST1R* protein levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0014] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount diminishes an adverse phenotype of lung disorder in the subject. The lung disorder may include chronic obstructive pulmonary disease (COPD), acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), cough, lung cancer, interstitial lung disease, or pulmonary fibrosis. In some embodiments, the adverse phenotype is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as

compared to prior to administration. In some embodiments, the adverse phenotype is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0015] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount enhances a protective phenotype of a lung disorder. The lung disorder may include chronic obstructive pulmonary disease (COPD), acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), cough, lung cancer, interstitial lung disease, or pulmonary fibrosis. In some embodiments, the protective phenotype is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by about 10% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 10%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, or 1000%, or by a range defined by any of the two aforementioned percentages.

[0016] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount improves (e.g. increases) a lung function measurement. The lung function measurement may include a measurement of forced expiratory volume in 1 second (FEV1), forced expiratory volume in 1 second percent predicted (FEV1pp), forced vital capacity (FVC), FEV1/FVC ratio, forced expiratory volume, or peak expiratory flow. In some embodiments, the lung function measurement is improved by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the lung function measurement is improved by about 10% or more, as compared to prior to administration. In some embodiments, the lung

function measurement is improved by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% or more, as compared to prior to administration. In some embodiments, the lung function measurement is improved by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, as compared to prior to administration. In some embodiments, the lung function measurement is improved by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the lung function measurement is improved by no more than about 10%, as compared to prior to administration. In some embodiments, the lung function measurement is improved by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the lung function measurement is improved by no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, as compared to prior to administration. In some embodiments, the lung function measurement is improved by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, or 1000%, or by a range defined by any of the two aforementioned percentages.

[0017] A leukocyte measurement may be affected by a lung disorder. For example, some inflammatory lung disorders that may include chronic obstructive pulmonary disease (COPD) or asthma may lead to increased inflammation and circulating white blood cell counts that may be treated using a composition comprising an oligonucleotide; or lung inflammation concomitant with a lung disorder may include an increase in leukocytes in a lung tissue or lung fluid (e.g. bronchoalveolar fluid). In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount changes a leukocyte measurement in a cell, fluid or tissue of the subject. In some embodiments, the cell is a lung cell, lung epithelial cell, type I or II alveolar cell, macrophage, alveolar macrophage, goblet cell, club cell, or fibroblast. In some embodiments, the tissue is lung tissue. In some embodiments, the fluid is a blood, serum, or plasma sample. In some embodiments, the fluid is a lung fluid such as a bronchoalveolar fluid. The change may be a decrease (for example, when circulating levels of leukocytes, or levels of leukocytes in lungs are increased due to an inflammatory lung disorder). The change may be an increase in some embodiments. In some embodiments, the leukocyte measurement is changed by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the leukocyte measurement is changed by about 10% or more, as compared to prior to administration. In some embodiments, the leukocyte measurement is changed by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, or about 80% or more, as compared to prior to administration. In some embodiments, the leukocyte measurement is changed by no more than about 2.5%, no more than about 5%, or no more

than about 7.5%, as compared to prior to administration. In some embodiments, the leukocyte measurement is changed by no more than about 10%, as compared to prior to administration. In some embodiments, the leukocyte measurement is changed by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the leukocyte measurement is changed by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, or by a range defined by any of the two aforementioned percentages.

[0018] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases chronic obstructive pulmonary disease (COPD) exacerbations in the subject. In some embodiments, the COPD exacerbations are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the COPD exacerbations are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the COPD exacerbations are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the COPD exacerbations are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the COPD exacerbations are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the COPD exacerbations are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the COPD exacerbations are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0019] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases asthma exacerbations in the subject. In some embodiments, the asthma exacerbations are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the asthma exacerbations are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the asthma exacerbations are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the asthma exacerbations are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the asthma exacerbations are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the asthma exacerbations are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than

about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the asthma exacerbations are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

A. siRNAs

[0020] In some embodiments, the composition comprises an oligonucleotide that targets *MST1R*, wherein the oligonucleotide comprises a small interfering RNA (siRNA). In some embodiments, the composition comprises an oligonucleotide that targets *MST1R*, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand.

[0021] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand is 12-30 nucleosides in length. In some embodiments, the composition comprises a sense strand that is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. The sense strand may be 14-30 nucleosides in length. In some embodiments, the composition comprises an antisense strand is 12-30 nucleosides in length. In some embodiments, the composition comprises an antisense strand that is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. The antisense strand may be 14-30 nucleosides in length.

[0022] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of a full-length human *MST1R* mRNA sequence such as SEQ ID NO: 9818. In some embodiments, at least one of the sense strand and the antisense strand comprise a nucleoside sequence comprising at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of SEQ ID NO: 9818.

[0023] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a double-stranded RNA duplex. In some embodiments, the first base pair of the double-stranded RNA duplex is an AU base pair.

[0024] In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the sense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned

numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides.

[0025] In some embodiments, the antisense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides.

[0026] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 19mer in a human *MST1R* mRNA. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a human *MST1R* mRNA.

[0027] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 17mer in a non-human primate *MST1R* mRNA. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a non-human primate *MST1R* mRNA.

[0028] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a human *MST1R* mRNA and less than or equal to 20 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 10 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 30 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 40 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 50 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 10 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 20 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 30 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 40 human off-targets, with no more than 3 mismatches in the antisense strand. In

some embodiments, the siRNA binds with a human *MST1R* mRNA and less than or equal to 50 human off-targets, with no more than 3 mismatches in the antisense strand.

[0029] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, siRNA binds with a human *MST1R* mRNA target site that does not harbor an SNP, with a minor allele frequency (MAF) greater or equal to 1% (pos. 2-18). In some embodiments, the MAF is greater or equal to about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20%.

[0030] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-4754, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-4754, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the sense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-4754, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-4754.

[0031] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 4755-9508, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand sequence comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 4755-9508, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand further comprises a 3' overhang. In some

embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 4755-9508, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 4755-9508.

[0032] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any one of **Tables 3-8**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any one of **Tables 3-8**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any one of **Tables 3-8**. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0033] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0034] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0035] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0036] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0037] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0038] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset F, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset F, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset F. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) *MST1R* mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

B. ASOs

[0039] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. In some embodiments, the ASO is 14-30 nucleosides in length. In some embodiments, the ASO is at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the

two aforementioned numbers. In some embodiments, the ASO is 15-25 nucleosides in length. In some embodiments, the ASO is 20 nucleosides in length.

[0040] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and comprising a nucleoside sequence complementary to about 12-30 contiguous nucleosides of a full-length human *MST1R* mRNA sequence such as SEQ ID NO: 9818; wherein (i) the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier. In some embodiments, the ASO comprise a nucleoside sequence complementary to at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of SEQ ID NO: 9818.

C. Modification patterns

[0041] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier. In some embodiments, the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. A phosphorothioate may include a nonbridging oxygen atom in a phosphate backbone of the oligonucleotide that is replaced by sulfur. Modified internucleoside linkages may be included in siRNAs or ASOs. Benefits of the modified internucleoside linkage may include decreased toxicity or improved pharmacokinetics.

[0042] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises a modified internucleoside linkage, 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, or a range of modified internucleoside linkages defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 18 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises no more than 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises 2 or more modified internucleoside linkages, 3 or more modified internucleoside linkages, 4 or more modified internucleoside linkages, 5 or more modified internucleoside linkages, 6 or more modified internucleoside linkages, 7 or more modified internucleoside linkages, 8 or more modified internucleoside linkages, 9 or more modified internucleoside linkages, 10 or more modified internucleoside linkages, 11 or more modified internucleoside linkages, 12 or more modified internucleoside linkages, 13 or more modified internucleoside linkages, 14 or more modified internucleoside linkages, 15 or more modified internucleoside linkages, 16 or more modified internucleoside linkages, 17 or more modified

internucleoside linkages, 18 or more modified internucleoside linkages, 19 or more modified internucleoside linkages, or 20 or more modified internucleoside linkages.

[0043] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises the modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises HLA. In some embodiments, the modified nucleoside comprises CeNA. In some embodiments, the modified nucleoside comprises a 2'-methoxyethyl group. In some embodiments, the modified nucleoside comprises a 2'-O-alkyl group. In some embodiments, the modified nucleoside comprises a 2'-O-allyl group. In some embodiments, the modified nucleoside comprises a 2'-fluoro group. In some embodiments, the modified nucleoside comprises a 2'-deoxy group. In some embodiments, the modified nucleoside comprises a 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. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside. In some embodiments, the modified nucleoside comprises a 2'-deoxyfluoro nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-NMA nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-DMAEOE nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-aminopropyl (2'-O-AP) nucleoside. In some embodiments, the modified nucleoside comprises 2'-ara-F. In some embodiments, the modified nucleoside comprises one or more 2' fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. Benefits of the modified nucleoside may include decreased toxicity or improved pharmacokinetics.

[0044] In some embodiments, 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, or a range of nucleosides defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 19 modified nucleosides. In some embodiments, the oligonucleotide comprises no more than 21 modified nucleosides. In some embodiments, the oligonucleotide comprises 2 or more modified nucleosides, 3 or more modified nucleosides, 4 or more modified nucleosides, 5 or more modified nucleosides, 6 or more modified nucleosides, 7 or more modified nucleosides, 8 or more modified nucleosides, 9 or more modified nucleosides, 10 or more modified nucleosides, 11 or more modified nucleosides, 12 or more modified nucleosides, 13 or more modified nucleosides, 14 or more modified nucleosides, 15 or more modified nucleosides, 16 or more modified nucleosides, 17 or more modified nucleosides, 18 or more modified nucleosides, 19 or more modified nucleosides, 20 or more modified nucleosides, or 21 or more modified nucleosides.

[0045] The oligonucleotide may be chemically conjugated to a targeting group, lipid (including, but not limited to cholesterol, cholesteryl derivatives, and fatty acids), nanoparticle, polymer, liposome, micelle,

or other delivery system. A targeting group may be linked to a 3' or 5' end of the oligonucleotide (e.g. to a 3' or 5' end of a sense strand or an antisense strand). In some embodiments, a targeting group is linked internally to a nucleotide on a sense strand or an antisense strand of the oligonucleotide. In some embodiments, a targeting group is linked to the oligonucleotide via a linker.

[0046] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises a moiety attached at a 3' or 5' terminus of the oligonucleotide. Examples of moieties include an integrin targeting ligand, a hydrophobic moiety, a sugar moiety, or a combination thereof. In some embodiments, the oligonucleotide is an siRNA having a sense strand, and the moiety is attached to a 5' end of the sense strand. In some embodiments, the oligonucleotide is an siRNA having a sense strand, and the moiety is attached to a 3' end of the sense strand. In some embodiments, the oligonucleotide is an siRNA having an antisense strand, and the moiety is attached to a 5' end of the antisense strand. In some embodiments, the oligonucleotide is an siRNA having an antisense strand, and the moiety is attached to a 3' end of the antisense strand. In some embodiments, the oligonucleotide is an ASO, and the moiety is attached to a 5' end of the ASO. In some embodiments, the oligonucleotide is an ASO, and the moiety is attached to a 3' end of the ASO.

[0047] In some embodiments, the oligonucleotide is delivered to a cell or tissue by linking the oligonucleotide to a targeting group. In some embodiments, the targeting group includes a cell receptor ligand, such as an integrin targeting ligand. Integrins may include a family of transmembrane receptors that facilitate cell-extracellular matrix (ECM) adhesion. In some embodiments, the moiety includes an epithelial-specific integrin. Integrin alpha-v-beta-6 ($\alpha\beta6$) may be an example of an epithelial-specific integrin. Integrin $\alpha\beta6$ may be a receptor for an ECM protein or TGF-beta latency-associated peptide (LAP). Integrin $\alpha\beta6$ may be expressed in a cell or tissue. Integrin $\alpha\beta6$ may be expressed or upregulated in injured pulmonary epithelium.

[0048] In some embodiments, the oligonucleotide is linked to an integrin targeting ligand that has affinity for integrin $\alpha\beta6$. An integrin targeting ligand may include a compound that has affinity for integrin $\alpha\beta6$ or integrin alpha-v-beta-3 ($\alpha\beta3$), may be useful as a ligand to facilitate targeting or delivery of the oligonucleotide to which it is attached to a particular cell type or tissue (e.g., to cells expressing integrin $\alpha\beta3$ or $\alpha\beta6$). In some embodiments, multiple integrin targeting ligands are linked to the oligonucleotide. In some embodiments, the oligonucleotide-integrin targeting ligand conjugates are selectively internalized by lung epithelial cells, either through receptor-mediated endocytosis or by other means.

[0049] Examples of targeting groups useful for delivering the oligonucleotide that include integrin targeting ligands may be based upon peptides or peptide mimics containing an arginine-glycine-aspartic acid (RGD) peptide. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an RGD peptide. In some embodiments, the composition comprises an RGD peptide. In some embodiments, the composition comprises an RGD peptide derivative. In some embodiments, the RGD peptide is attached at a 3' terminus of the oligonucleotide. In some embodiments, the RGD peptide is attached at a 5' terminus of the oligonucleotide. In some embodiments, the composition comprises a sense strand, and the RGD peptide is

attached to the sense strand (e.g. attached to a 5' end of the sense strand, or attached to a 3' end of the sense strand). In some embodiments, the composition comprises an antisense strand, and the RGD peptide is attached to the antisense strand (e.g. attached to a 5' end of the antisense strand, or attached to a 3' end of the antisense strand). In some embodiments, the composition comprises an RGD peptide attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the oligonucleotide comprises an RGD peptide and a lipid attached at a 3' or 5' terminus of the oligonucleotide. The RGD peptide may be linear. The RGD peptide may be cyclic. An RGD peptide may include a D-amino acid. In some embodiments, the RGD peptide comprises Cyclo(-Arg-Gly-Asp-D-Phe-Cys) (SEQ ID NO: 9837). In some embodiments, the RGD peptide comprises Cyclo(-Arg-Gly-Asp-D-Phe-Lys) (SEQ ID NO: 9838). In some embodiments, the RGD peptide comprises Cyclo(-Arg-Gly-Asp-D-Phe-azido) (SEQ ID NO: 9839). In some embodiments, the RGD peptide comprises an amino benzoic acid derived RGD. In some embodiments, the RGD peptide comprises Cyclo(-Arg-Gly-Asp-D-Phe-Cys) (SEQ ID NO: 9837), Cyclo(-Arg-Gly-Asp-D-Phe-Lys) (SEQ ID NO: 9838), Cyclo(-Arg-Gly-Asp-D-Phe-azido) (SEQ ID NO: 9839), an amino benzoic acid derived RGD, or a combination thereof. In some embodiments, the RGD peptide comprises multiple of such RGD peptides. For example, the RGD peptide may include 2, 3, or 4 RGD peptides. Some embodiments include an arginine-glycine-glutamic acid peptide.

[0050] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises a hydrophobic moiety. The hydrophobic moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The hydrophobic moiety may include a lipid such as a fatty acid. The hydrophobic moiety may include a hydrocarbon. The hydrocarbon may be linear. The hydrocarbon may be non-linear. The hydrophobic moiety may include a lipid moiety or a cholesterol moiety, or a combination thereof.

[0051] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl, stearyl, or α -tocopherol, or a combination thereof.

[0052] The oligonucleotide may include purines. Examples of purines include adenine (A) or guanine (G), or modified versions thereof. The oligonucleotide may include pyrimidines. Examples of pyrimidines include cytosine (C), thymine (T), or uracil (U), or modified versions thereof.

[0053] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. 2'-O-methyl may include 2' O-methyl. Where a 2' O-methyl modification is included, it is contemplated that a 2' methyl modification may be included, and vice versa.

[0055] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines, and pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and purines of the oligonucleotide comprise 2' fluoro modified purines.

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[0057] In some cases, the oligonucleotide comprises a particular modification pattern. In some embodiments, position 9 counting from the 5' end of the of a strand of the oligonucleotide may have a 2'F modification. In some embodiments, when position 9 of a strand of the oligonucleotide is a pyrimidine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[0058] In some embodiments, when position 9 of a strand of the oligonucleotide is a purine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are purines, then both of these purines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[0059] In some cases, position 9 of a strand of the oligonucleotide can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of a strand of the oligonucleotide. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to these a strand of the oligonucleotide rules.

[0060] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines.

In some embodiments, 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2' fluoro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine; all purines of the sense strand comprises 2'-O-methyl modified purines; 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2' fluoro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides.

[0061] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2' fluoro-modified purine, provided there are not three 2' fluoro-modified purine in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine; all pyrimidine of the sense strand comprises 2'-O-methyl modified pyrimidines; 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2' fluoro-modified purines, provided there are not three 2' fluoro-modified purines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, there are not three 2' fluoro-modified purines in a row. In some embodiments, there are not three 2' fluoro-modified pyrimidines in a row.

[0062] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2' fluoro-modified nucleotides. In some embodiments, all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2' fluoro-modified purines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified

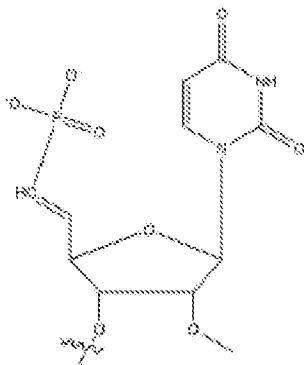
deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2' fluoro-modified nucleotides; all pyrimidines in positions 10 to 21 of the sense strand comprise 2' -O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2' -O-methyl modified purines or 2' fluoro-modified purines; the odd-numbered positions of the antisense strand comprise 2' -O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides.

[0063] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2' fluoro-modified nucleotides. In some embodiments, all purines in positions 10 to 21 of the sense strand comprise 2' -O-methyl modified purines and all pyrimidines in positions 10 to 21 of the comprise 2' -O-methyl modified pyrimidines or 2' fluoro-modified pyrimidines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2' -O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2' -O-methyl modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2' fluoro-modified nucleotides; all purines in positions 10 to 21 of the sense strand comprise 2' -O-methyl modified purines and all pyrimidines in positions 10 to 21 of the comprise 2' -O-methyl modified pyrimidines or 2' fluoro-modified pyrimidines; the odd-numbered positions of the antisense strand comprise 2' -O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotide.

[0064] In some embodiments, the moiety includes a negatively charged group attached at a 5' end of the oligonucleotide. This may be referred to as a 5'-end group. In some embodiments, the negatively charged group is attached at a 5' end of an antisense strand of an siRNA disclosed herein. The 5'-end group may be or include a 5'-end phosphorothioate, 5'-end phosphorodithioate, 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate, 5'-end cyclopropyl phosphonate, or a 5'-deoxy-5'-C-malonyl. The 5'-end group may comprise 5'-VP. In some embodiments, the 5'-VP comprises a trans-vinylphosphate or cis-vinylphosphate. The 5'-end group may include an extra 5' phosphate. A combination of 5'-end groups may be used.

[0065] In some embodiments, the oligonucleotide includes a negatively charged group. The negatively charged group may aid in cell or tissue penetration. The negatively charged group may be attached at a 5' or 3' end (e.g. a 5' end) of the oligonucleotide. This may be referred to as an end group. The end group may be or include a phosphorothioate, phosphorodithioate, vinylphosphonate, methylphosphonate, cyclopropyl phosphonate, or a deoxy-C-malonyl. The end group may include an extra 5' phosphate such as an extra 5' phosphate. A combination of end groups may be used.

[0066] In some embodiments, the oligonucleotide includes a phosphate mimic. In some embodiments, the phosphate mimic comprises vinyl phosphonate. In some embodiments, the vinyl phosphonate comprises a trans-vinylphosphate. In some embodiments, the vinyl phosphonate comprises a cis-vinylphosphate. An example of a nucleotide that includes a vinyl phosphonate is shown below.



5' vinylphosphonate 2' O Methyl Uridine

[0067] In some embodiments, the vinyl phosphonate increases the stability of the oligonucleotide. In some embodiments, the vinyl phosphonate increases the accumulation of the oligonucleotide in tissues. In some embodiments, the vinyl phosphonate protects the oligonucleotide from an exonuclease or a phosphatase. In some embodiments, the vinyl phosphonate improves the binding affinity of the oligonucleotide with the siRNA processing machinery.

[0068] In some embodiments, the oligonucleotide includes 1 vinyl phosphonate. In some embodiments, the oligonucleotide includes 2 vinyl phosphonates. In some embodiments, the oligonucleotide includes 3 vinyl phosphonates. In some embodiments, the oligonucleotide includes 4 vinyl phosphonates. In some embodiments, the antisense strand of the oligonucleotide comprises a vinyl phosphonate at the 5' end. In some embodiments, the antisense strand of the oligonucleotide comprises a vinyl phosphonate at the 3' end. In some embodiments, the sense strand of the oligonucleotide comprises a vinyl phosphonate at the 5' end. In some embodiments, the sense strand of the oligonucleotide comprises a vinyl phosphonate at the 3' end.

1. *Hydrophobic moieties*

[0069] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises a hydrophobic moiety. The hydrophobic moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The hydrophobic moiety may include a lipid such as a fatty acid. The hydrophobic moiety may include a hydrocarbon. The hydrocarbon may be linear. The hydrocarbon may be non-linear. The hydrophobic moiety may include a lipid moiety or a cholesterol moiety, or a combination thereof.

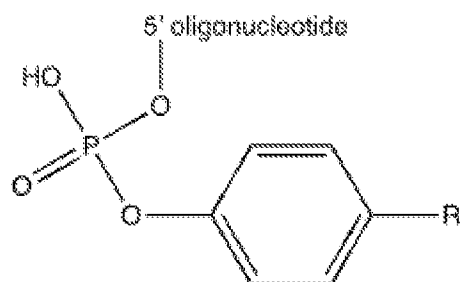
[0070] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl, stearyl, or α -tocopherol, or a combination thereof.

[0071] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises a hydrophobic ligand or moiety. In some embodiments, the hydrophobic ligand or moiety comprises cholesterol. In some embodiments, the hydrophobic ligand or moiety comprises a cholesterol derivative. In some embodiments, the hydrophobic ligand or moiety is attached at a 3' terminus of the oligonucleotide. In some embodiments, the hydrophobic ligand or moiety is attached at a 5' terminus of the oligonucleotide. In some embodiments, the composition comprises a sense strand, and the hydrophobic ligand or moiety is attached to the sense strand (e.g. attached to a 5' end of the sense strand, or attached to a 3' end of the sense strand). In some embodiments, the composition comprises an antisense strand, and the hydrophobic ligand or moiety is attached to the antisense strand (e.g. attached to a 5' end of the antisense strand, or attached to a 3' end of the antisense strand). In some embodiments, the composition comprises a hydrophobic ligand or moiety attached at a 3' or 5' terminus of the oligonucleotide.

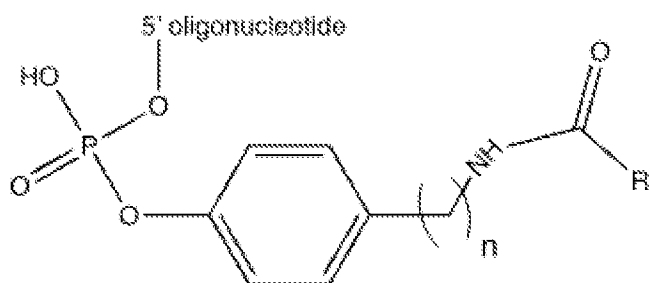
[0072] In some embodiments, a hydrophobic moiety is attached to the oligonucleotide (e.g. a sense strand and/or an antisense strand of a siRNA). In some embodiments, a hydrophobic moiety is attached at a 3' terminus of the oligonucleotide. In some embodiments, a hydrophobic moiety is attached at a 5' terminus of the oligonucleotide. In some embodiments, the hydrophobic moiety comprises cholesterol. In some embodiments, the hydrophobic moiety includes a cyclohexanyl.

[0073] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, a lipid is attached at a 3' terminus of the oligonucleotide. In some embodiments, a lipid is attached at a 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl, stearyl, or α -tocopherol, or a combination thereof. In some embodiments, the lipid comprises stearyl, lithocholyl, docosanyl, docosahexaenyl, or myristyl. In some embodiments, the lipid comprises cholesterol. In some embodiments, the lipid includes a sterol such as cholesterol. In some embodiments, the lipid comprises stearyl, t-butylphenol, n-butylphenol, octylphenol, dodecylphenol, phenyl n-dodecyl, octadecylbenzamide, hexadecylbenzamide, or octadecylcyclohexyl. In some embodiments, the lipid comprises phenyl para C12.

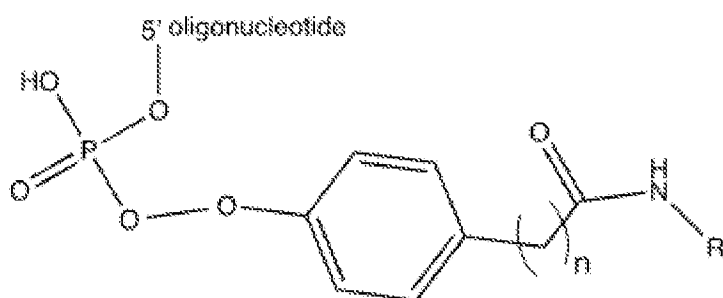
[0074] In some embodiments, the oligonucleotide comprises any aspect of the following structure:



[0075] In some embodiments, the oligonucleotide comprises any aspect of the following structure:



[0076] In some embodiments, the oligonucleotide comprises any aspect of the following structure:



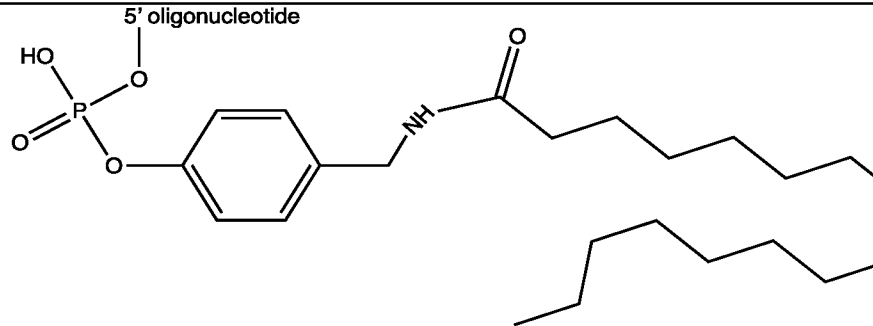
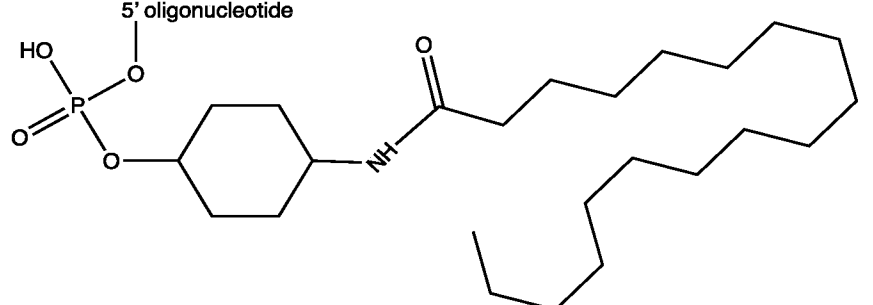
[0077] In some embodiments, the oligonucleotide comprises any aspect of the following structure: The aspect included in the oligonucleotide may include the entire structure, or may include the lipid moiety, of any of the structures shown. In some embodiments, n is 1-3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, the alkyl group contains 4-18 carbons. In some embodiments, the lipid moiety comprises an alcohol or ether.

[0078] In some embodiments, the lipid includes a fatty acid. In some embodiments, the lipid comprises a lipid depicted in **Table 1**. The example lipid moieties in **Table 1** are shown attached at a 5' end of an oligonucleotide, in which the 5' terminal phosphate of the oligonucleotide is shown with the lipid moiety. In some embodiments, a lipid moiety in **Table 1** may be attached at a different point of attachment than shown. For example, the point of attachment of any of the lipid moieties in the table may be at a 3' oligonucleotide end. In some embodiments, the lipid is used for targeting the oligonucleotide to a non-hepatic cell or tissue.

Table 1: Hydrophobic moiety examples

Hydrophobic Moiety Description	Hydrophobic Moiety Name	Example Conjugation
stearyl	ETL3	The diagram shows a phosphate group (P=O, OH, O-) attached to a 5' oligonucleotide (represented by a wavy line). The phosphate is linked via an oxygen atom to a long, zigzag hydrocarbon chain representing the stearyl moiety.

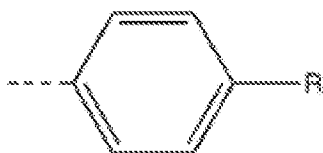
t-butylphenyl	ETL7	
n-butylphenyl	ETL8	
octylphenyl	ETL9	
dodecylphenyl	ETL10	
phenyl n-dodecyl	ETL12	
octadecylbenzamide	ETL13	

hexadecylbenzamide	ETL15	
octadecylcyclohexyl	ETL16	

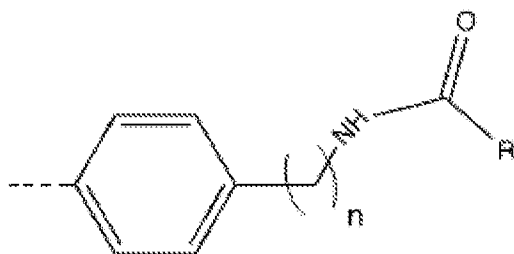
[0079] In some embodiments, the lipid or lipid moiety includes 16 to 18 carbons. In some embodiments, the lipid includes 16 carbons. In some embodiments, the lipid includes 17 carbons. In some embodiments, the lipid includes 18 carbons. In some embodiments, the lipid moiety includes 16 carbons. In some embodiments, the lipid moiety includes 17 carbons. In some embodiments, the lipid moiety includes 18 carbons.

[0080] The hydrophobic moiety may include a linker that comprises a carbocycle. The carbocycle may be six-membered. Some examples of a carbocycle include phenyl or cyclohexyl. The linker may include a phenyl. The linker may include a cyclohexyl. The lipid may be attached to the carbocycle, which may in turn be attached at a phosphate (e.g. 5' or 3' phosphate) of the oligonucleotide. In some embodiments, the lipid or hydrocarbon, and the end of the sense are connected to the phenyl or cyclohexyl linker in the 1,4; 1,3; or 1,2 substitution pattern (e.g. the para, meta, or ortho phenyl configuration). In some embodiments, the lipid or hydrocarbon, and the end of the sense are connected to the phenyl or cyclohexyl linker in the 1,4 substitution pattern (e.g. the para phenyl configuration). The lipid may be attached to the carbocycle in the 1,4 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the 1,3 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the 1,2 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the ortho orientation relative to the oligonucleotide. The lipid may be attached to the carbocycle in the para orientation relative to the oligonucleotide. The lipid may be attached to the carbocycle in the meta orientation relative to the oligonucleotide.

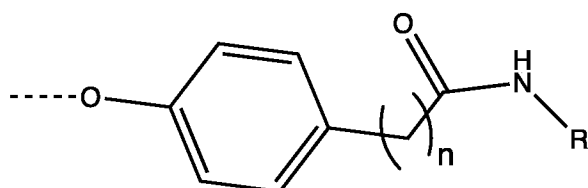
[0081] The lipid moiety may comprise or consist of the following structure:



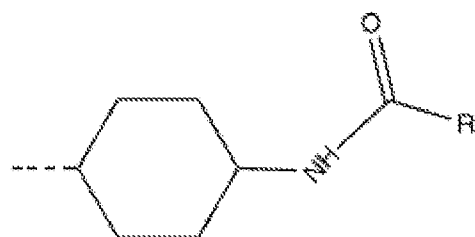
[0082] In some embodiments, the lipid moiety comprises or consists of the following structure:



[0083] In some embodiments, the lipid moiety comprises the following structure:



[0084] In some embodiments, the lipid moiety comprises or consist of the following structure:



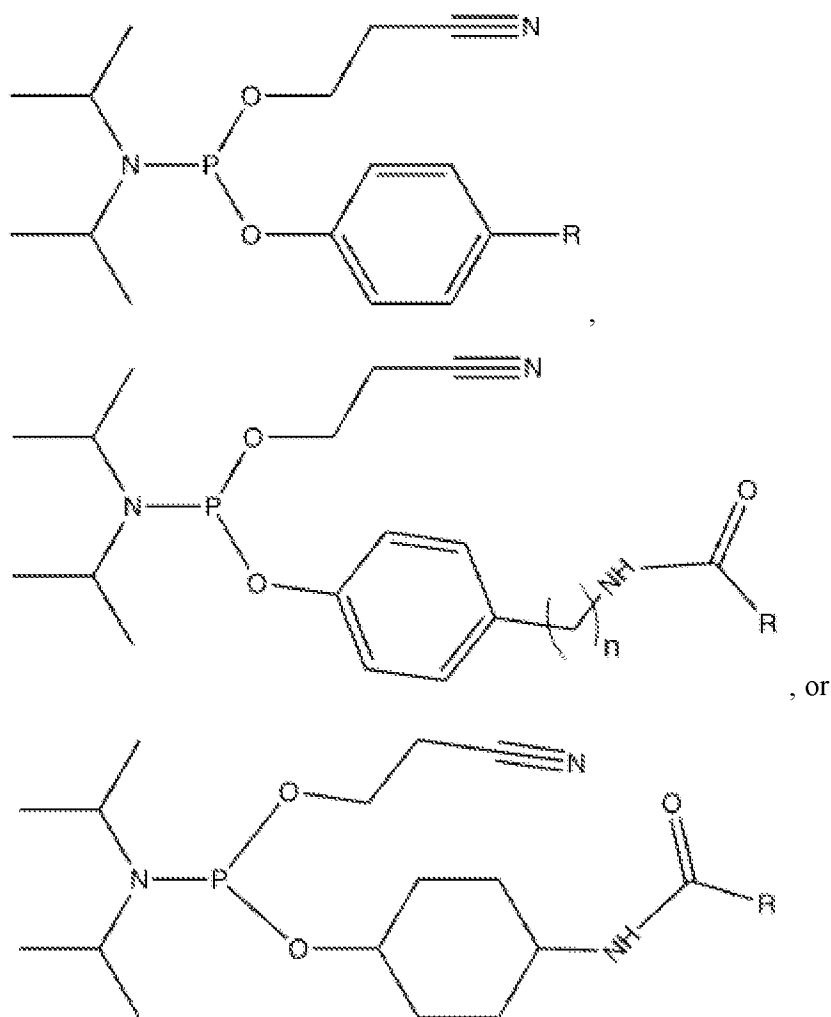
[0085] In some embodiments, the dotted line indicates a covalent connection. The covalent connection may be between an end of the sense or antisense strand. For example, the connection may be to the 5' end of the sense strand. In some embodiments, n is 0-3. In some embodiments, n is 1-3. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, R comprises or consists of an alkyl group containing 4-18 carbons.

[0086] The lipid moiety may be attached at a 5' end of the oligonucleotide. The 5' end may have one phosphate linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have two phosphates linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have three phosphates linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have one phosphate connected to the 5' carbon of a sugar of the oligonucleotide, where the one phosphate is connected to the lipid moiety. The 5' end may have two phosphates connected to the 5' carbon of a sugar of the oligonucleotide, where the one of the two phosphates is connected to the lipid moiety. The 5' end may have three phosphates connected to the 5' carbon of a sugar of the oligonucleotide, where the one of the three phosphates is connected to the lipid moiety. The sugar may include a ribose. The sugar may include a deoxyribose. The sugar may be modified a such as a 2'

modified sugar (e.g. a 2' O-methyl or 2' fluoro ribose). A phosphate of the 5' end may include a modification such as a sulfur in place of an oxygen. Two phosphates of the 5' end may include a modification such as a sulfur in place of an oxygen. Three phosphates of the 5' end may include a modification such as a sulfur in place of an oxygen.

[0087] In some embodiments, the oligonucleotide includes 1 lipid moiety. In some embodiments, the oligonucleotide includes 2 lipid moieties. In some embodiments, the oligonucleotide includes 3 lipid moieties. In some embodiments, the oligonucleotide includes 4 lipid moieties.

[0088] Some embodiments relate to a method of making an oligonucleotide comprising a hydrophobic conjugate. A strategy for making hydrophobic conjugates may include use of a phosphoramidite reagent based upon a 6-membered ring alcohol such as a phenol or cyclohexanol. The phosphoramidite may be reacted to a nucleotide to connect the nucleotide to the hydrophobic moiety, and thereby produce the hydrophobic conjugate. Some examples of phosphoramidite reagents that may be used to produce a hydrophobic conjugate are provided as follows:



[0089] In some embodiments, n is 1-3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, R comprises

or consists of an alkyl group containing 4-18 carbons. Any one of the phosphoramidite reagents may be reacted to a 5' end of an oligonucleotide to produce an oligonucleotide comprising a hydrophobic moiety. In some embodiments, the phosphoramidite reagents is reacted to a 5' end of a sense strand of an siRNA. The sense strand may then be hybridized to an antisense strand to form a duplex. The hybridization may be performed by incubating the sense and antisense strands in solution at a given temperature. The temperature may be gradually reduced. The temperature may comprise or include a temperature comprising an annealing temperature for the sense and antisense strands. The temperature may be below or include a temperature below the annealing temperature for the sense and antisense strands. The temperature may be below a melting temperature of the sense and antisense strands.

[0090] The lipid may be attached to the oligonucleotide by a linker. The linker may include a polyethyleneglycol (e.g. tetraethyleneglycol).

[0091] The modifications described herein may be useful for delivery to a cell or tissue, for example, extrahepatic delivery or targeting of an oligonucleotide composition. The modifications described herein may be useful for targeting an oligonucleotide composition to a cell or tissue.

2. *Sugar moieties*

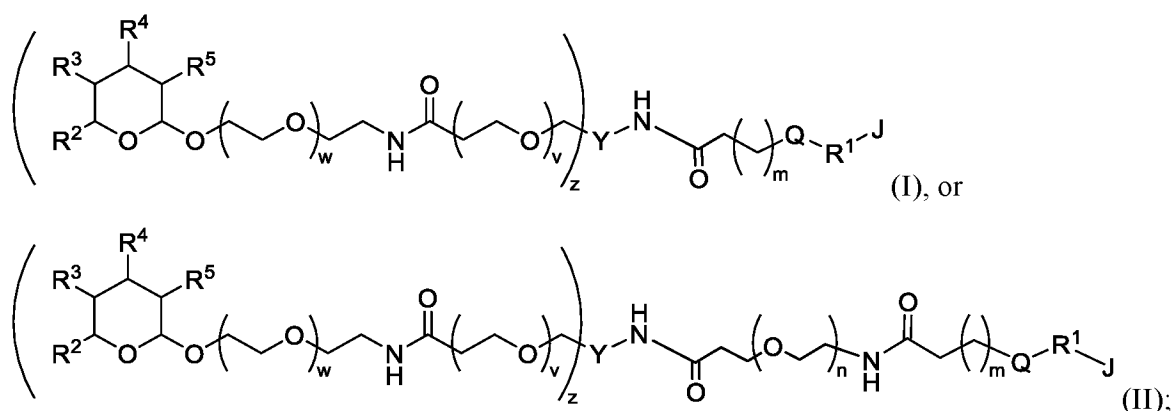
[0092] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises a sugar moiety. The sugar moiety may include an N-acetyl galactose moiety (e.g. an N-acetylgalactosamine (GalNAc) moiety), an N-acetyl glucose moiety (e.g. an N-acetylglucosamine (GlcNAc) moiety), a fucose moiety, or a mannose moiety. The sugar moiety may include 1, 2, 3, or more sugar molecules. The sugar moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The sugar moiety may include an N-acetyl galactose moiety. The sugar moiety may include an N-acetylgalactosamine (GalNAc) moiety. The sugar moiety may include an N-acetyl glucose moiety. The sugar moiety may include N-acetylglucosamine (GlcNAc) moiety. The sugar moiety may include a fucose moiety. The sugar moiety may include a mannose moiety. N-acetyl glucose, GlcNAc, fucose, or mannose may be useful for targeting macrophages when they target or bind a mannose receptor such as CD206. The sugar moiety may be useful for binding or targeting an asialoglycoprotein receptor such as an asialoglycoprotein receptor of a hepatocyte. The GalNAc moiety may bind to an asialoglycoprotein receptor. The GalNAc moiety may target a hepatocyte.

[0093] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) moiety. GalNAc may be useful for hepatocyte targeting. The GalNAc moiety may include a bivalent or trivalent branched linker. The oligo may be attached to 1, 2 or 3 GalNAcs through a bivalent or trivalent branched linker. The GalNAc moiety may include 1, 2, 3, or more GalNAc molecules. The GalNAc moiety may be attached at a 3' or 5' terminus of the oligonucleotide.

[0094] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) ligand for hepatocyte targeting. In some embodiments, the composition comprises GalNAc. In some embodiments, the composition comprises a GalNAc derivative. In some embodiments, the GalNAc ligand is attached at

a 3' terminus of the oligonucleotide. In some embodiments, the GalNAc ligand is attached at a 5' terminus of the oligonucleotide. In some embodiments, the composition comprises a sense strand, and the GalNAc ligand is attached to the sense strand (e.g. attached to a 5' end of the sense strand, or attached to a 3' end of the sense strand). In some embodiments, the composition comprises an antisense strand, and the GalNAc ligand is attached to the antisense strand (e.g. attached to a 5' end of the antisense strand, or attached to a 3' end of the antisense strand). In some embodiments, the composition comprises a GalNAc ligand attached at a 3' or 5' terminus of the oligonucleotide.

[0095] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that inhibits the expression of MST1R, wherein the oligonucleotide comprises a GalNAc moiety. The GalNAc moiety may be included in any formula, structure, or GalNAc moiety shown below. In some embodiments, described herein is a compound (e.g. oligonucleotide) represented by Formula (I) or (II):



or a salt thereof, wherein

J is an oligonucleotide;

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR⁶, or

if z is 1, Y is C(R⁶)₂;

Q is selected from:

C₃₋₁₀ carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -NO₂, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -C(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -N(R⁷)C(O)N(R⁷)₂, -OC(O)N(R⁷)₂, -N(R⁷)C(O)OR⁷, -C(O)OR⁷, -OC(O)R⁷, -S(O)R⁷, and C₁₋₆ alkyl, wherein the C₁₋₆ alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, and -NH₂;

R¹ is a linker selected from:

-O-, -S-, -N(R⁷)-, -C(O)-, -C(O)N(R⁷)-, -N(R⁷)C(O)-, -N(R⁷)C(O)N(R⁷)-, -OC(O)N(R⁷)-, -N(R⁷)C(O)O-, -C(O)O-, -OC(O)-, -S(O)-, -S(O)₂-, -OS(O)₂-, -OP(O)(OR⁷)O-, -SP(O)(OR⁷)O-, -

OP(S)(OR⁷)O-, -OP(O)(SR⁷)O-, -OP(O)(OR⁷)S-, -OP(O)(O⁻)O-, -SP(O)(O⁻)O-, -OP(S)(O⁻)O-, -
 OP(O)(S⁻)O-, -OP(O)(O⁻)S-, -OP(O)(OR⁷)NR⁷-, -OP(O)(N(R⁷)₂)NR⁷-, -OP(OR⁷)O-, -
 OP(N(R⁷)₂)O-, -OP(OR⁷)N(R⁷)-, and -OPN(R⁷)₂NR⁷-;

each R² is independently selected from:

C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -C(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -N(R⁷)C(O)N(R⁷)₂, -
 OC(O)N(R⁷)₂, -N(R⁷)C(O)OR⁷, -C(O)OR⁷, -OC(O)R⁷, and -S(O)R⁷;

R³ and R⁴ are each independently selected from:

-OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -C(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -N(R⁷)C(O)N(R⁷)₂, -
 OC(O)N(R⁷)₂, -N(R⁷)C(O)OR⁷, -C(O)OR⁷, -OC(O)R⁷, and -S(O)R⁷;

each R⁵ is independently selected from:

-OC(O)R⁷, -OC(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -N(R⁷)C(O)N(R⁷)₂, -
 N(R⁷)C(O)OR⁷, -C(O)R⁷, -C(O)OR⁷, and -C(O)N(R⁷)₂;

each R⁶ is independently selected from:

hydrogen;
 halogen, -CN, -NO₂, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -C(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -
 N(R⁷)C(O)N(R⁷)₂, -OC(O)N(R⁷)₂, -N(R⁷)C(O)OR⁷, -C(O)OR⁷, -OC(O)R⁷, and -S(O)R⁷; and
 C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -NO₂, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -C(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -
 N(R⁷)C(O)N(R⁷)₂, -OC(O)N(R⁷)₂, -N(R⁷)C(O)OR⁷, -C(O)OR⁷, -OC(O)R⁷, and -S(O)R⁷;

each R⁷ is independently selected from:

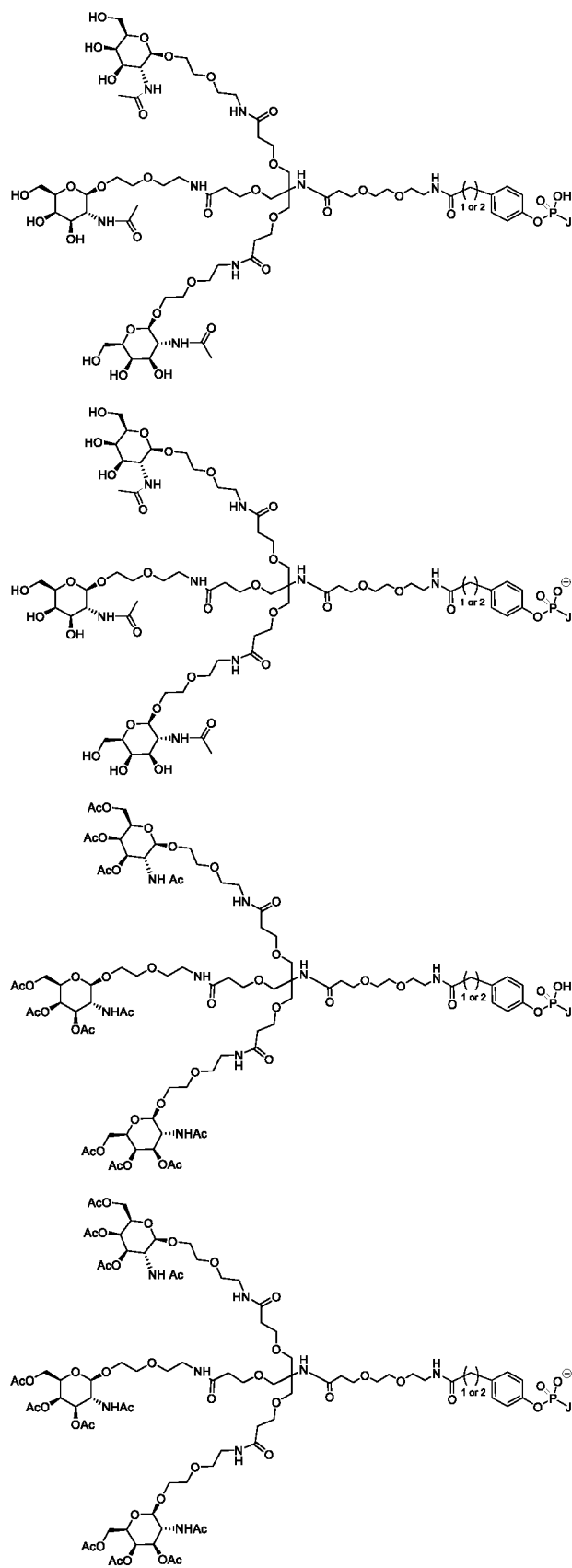
hydrogen;
 C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -
 O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-
 membered heterocycle; and
 C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -
 NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, and C₁₋₆ haloalkyl.

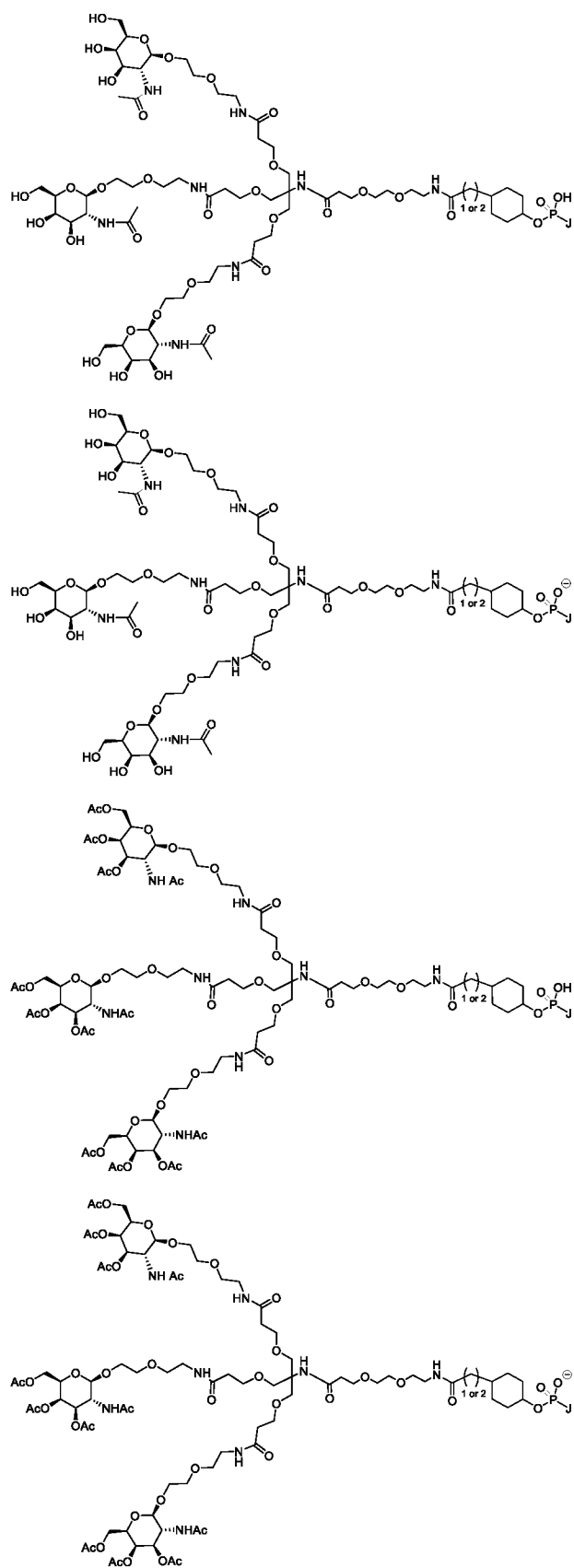
[0096] In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is 1. In some embodiments, each v is independently selected from any value from 1 to 10. In some embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is 1. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is 2. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from 1 and 2. In some embodiments, z is 3 and Y is C. In some embodiments,

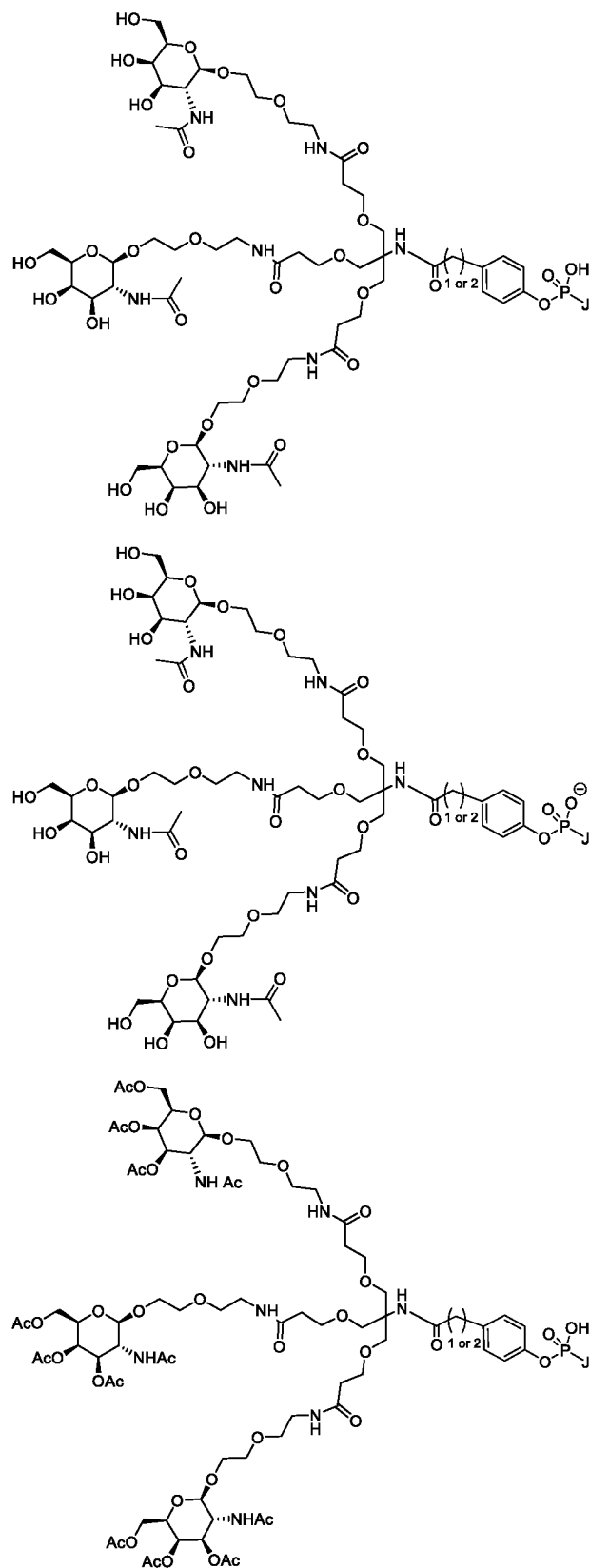
Q is selected from C₅₋₆ carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -NO₂, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -C(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -N(R⁷)C(O)N(R⁷)₂, -OC(O)N(R⁷)₂, -N(R⁷)C(O)OR⁷, -C(O)OR⁷, -OC(O)R⁷, and -S(O)R⁷. In some embodiments, Q is selected from C₅₋₆ carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, and -NH₂. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, and -NH₂. In some embodiments, Q is selected from phenyl. In some embodiments, Q is selected from cyclohexyl. In some embodiments, R¹ is selected from -OP(O)(OR⁷)O-, -SP(O)(OR⁷)O-, -OP(S)(OR⁷)O-, -OP(O)(SR⁷)O-, -OP(O)(OR⁷)S-, -OP(O)(O-)O-, -SP(O)(O-)O-, -OP(S)(O-)O-, -OP(O)(S-)O-, -OP(O)(O-)S-, -OP(O)(OR⁷)NR⁷-, -OP(O)(N(R⁷)₂)NR⁷-, -OP(OR⁷)O-, -OP(N(R⁷)₂)O-, -OP(OR⁷)N(R⁷)-, and -OPN(R⁷)₂NR⁷. In some embodiments, R¹ is selected from -OP(O)(OR⁷)O-, -SP(O)(OR⁷)O-, -OP(S)(OR⁷)O-, -OP(O)(SR⁷)O-, -OP(O)(OR⁷)S-, -OP(O)(O-)O-, -SP(O)(O-)O-, -OP(S)(O-)O-, -OP(O)(S-)O-, -OP(O)(O-)S-, and -OP(OR⁷)O-. In some embodiments, R¹ is selected from -OP(O)(OR⁷)O-, -OP(S)(OR⁷)O-, -OP(O)(O-)O-, -OP(S)(O-)O-, -OP(O)(S-)O-, and -OP(OR⁷)O-. In some embodiments, R¹ is selected from -OP(O)(OR⁷)O- and -OP(OR⁷)O-. In some embodiments, R² is selected from C₁₋₃ alkyl substituted with one or more substituents independently selected from halogen, -OR⁷, -OC(O)R⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, and -S(O)R⁷. In some embodiments, R² is selected from C₁₋₃ alkyl substituted with one or more substituents independently selected from -OR⁷, -OC(O)R⁷, -SR⁷, and -N(R⁷)₂. In some embodiments, R² is selected from C₁₋₃ alkyl substituted with one or more substituents independently selected from -OR⁷ and -OC(O)R⁷. In some embodiments, R³ is selected from halogen, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -OC(O)R⁷, and -S(O)R⁷. In some embodiments, R³ is selected from -OR⁷, -SR⁷, -OC(O)R⁷, and -N(R⁷)₂. In some embodiments, R³ is selected from -OR⁷ and -OC(O)R⁷. In some embodiments, R⁴ is selected from halogen, -OR⁷, -SR⁷, -N(R⁷)₂, -C(O)R⁷, -OC(O)R⁷, and -S(O)R⁷. In some embodiments, R⁴ is selected from -OR⁷, -SR⁷, -OC(O)R⁷, and -N(R⁷)₂. In some embodiments, R⁴ is selected from -OR⁷ and -OC(O)R⁷. In some embodiments, R⁵ is selected from -OC(O)R⁷, -OC(O)N(R⁷)₂, -N(R⁷)C(O)R⁷, -N(R⁷)C(O)N(R⁷)₂, and -N(R⁷)C(O)OR⁷. In some embodiments, R⁵ is selected from -OC(O)R⁷ and -N(R⁷)C(O)R⁷. In some embodiments, each R⁷ is independently selected from: hydrogen; and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, or 3- to 10-membered heterocycle. In some embodiments, each R⁷ is independently selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, and -NH(C₁₋₆ alkyl). In some embodiments, each R⁷ is independently selected from C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH. In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, and C₁₋₃ alkyl; R¹ is

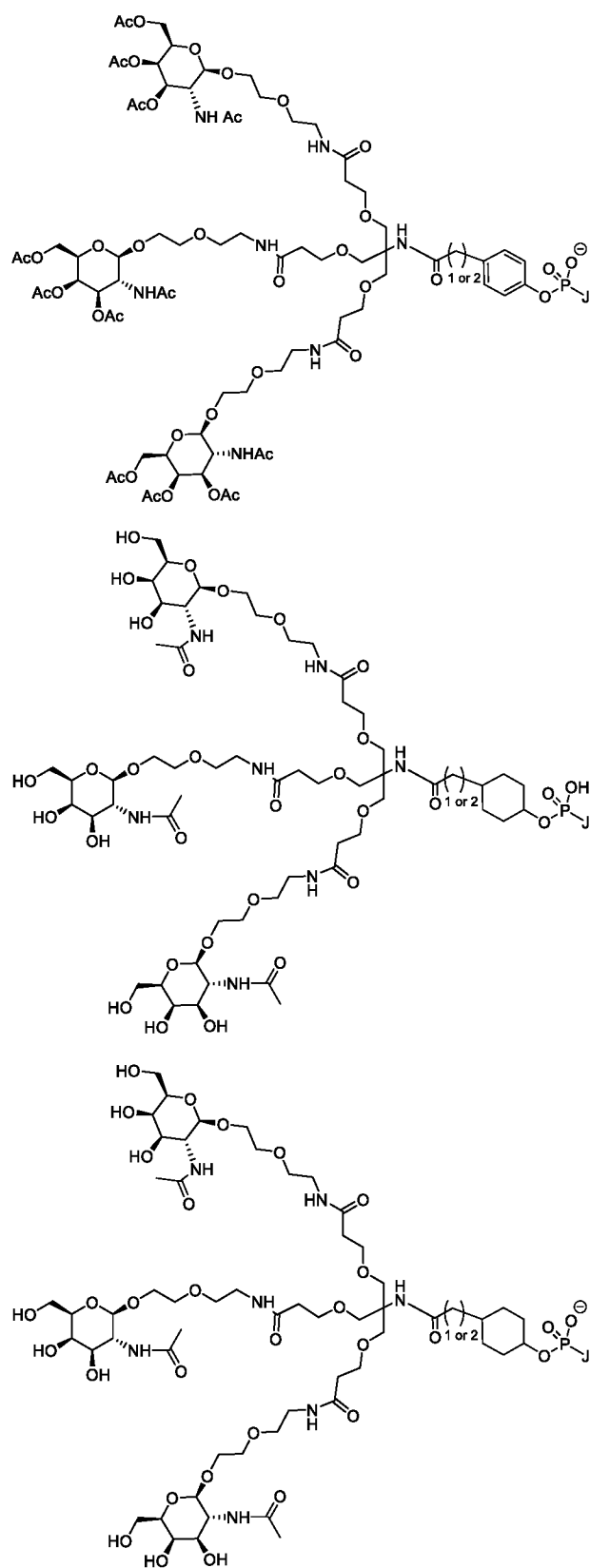
selected from $-\text{OP}(\text{O})(\text{OR}^7)\text{O}-$, $-\text{OP}(\text{S})(\text{OR}^7)\text{O}-$, $-\text{OP}(\text{O})(\text{O}^-)\text{O}-$, $-\text{OP}(\text{S})(\text{O}^-)\text{O}-$, $-\text{OP}(\text{O})(\text{S}^-)\text{O}-$, and $-\text{OP}(\text{OR}^7)\text{O}-$; R^2 is C_1 alkyl substituted with $-\text{OH}$ or $-\text{OC}(\text{O})\text{CH}_3$;

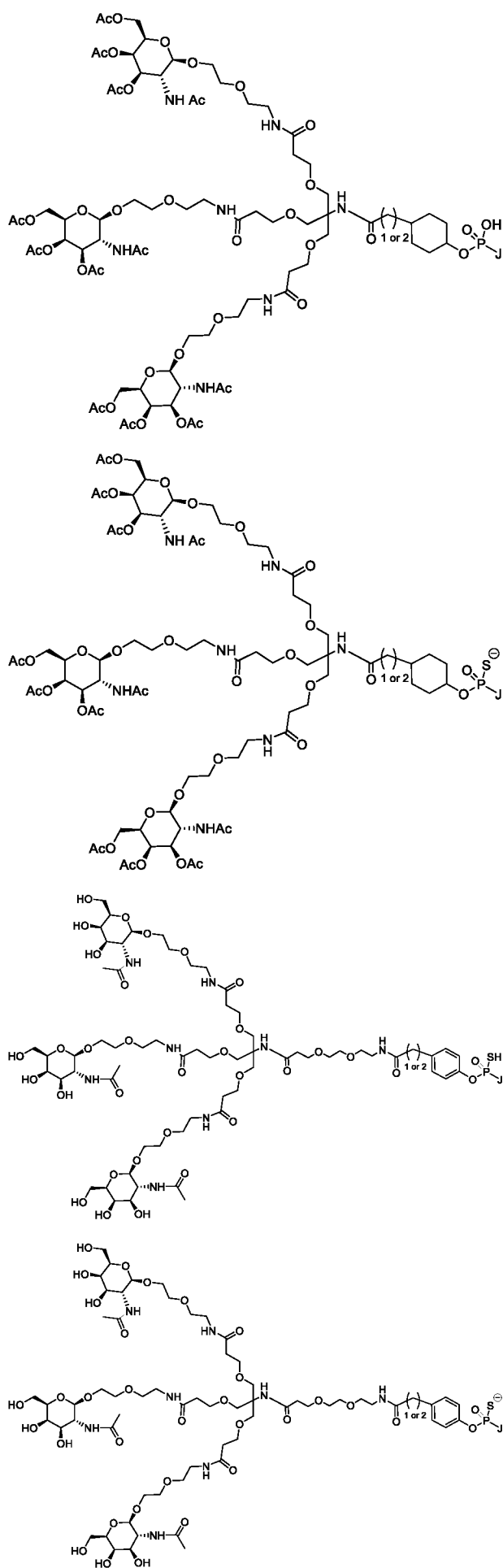
R^3 is $-\text{OH}$ or $-\text{OC}(\text{O})\text{CH}_3$; R^4 is $-\text{OH}$ or $-\text{OC}(\text{O})\text{CH}_3$; and R^5 is $-\text{NH}(\text{O})\text{CH}_3$. In some embodiments, the compound comprises:

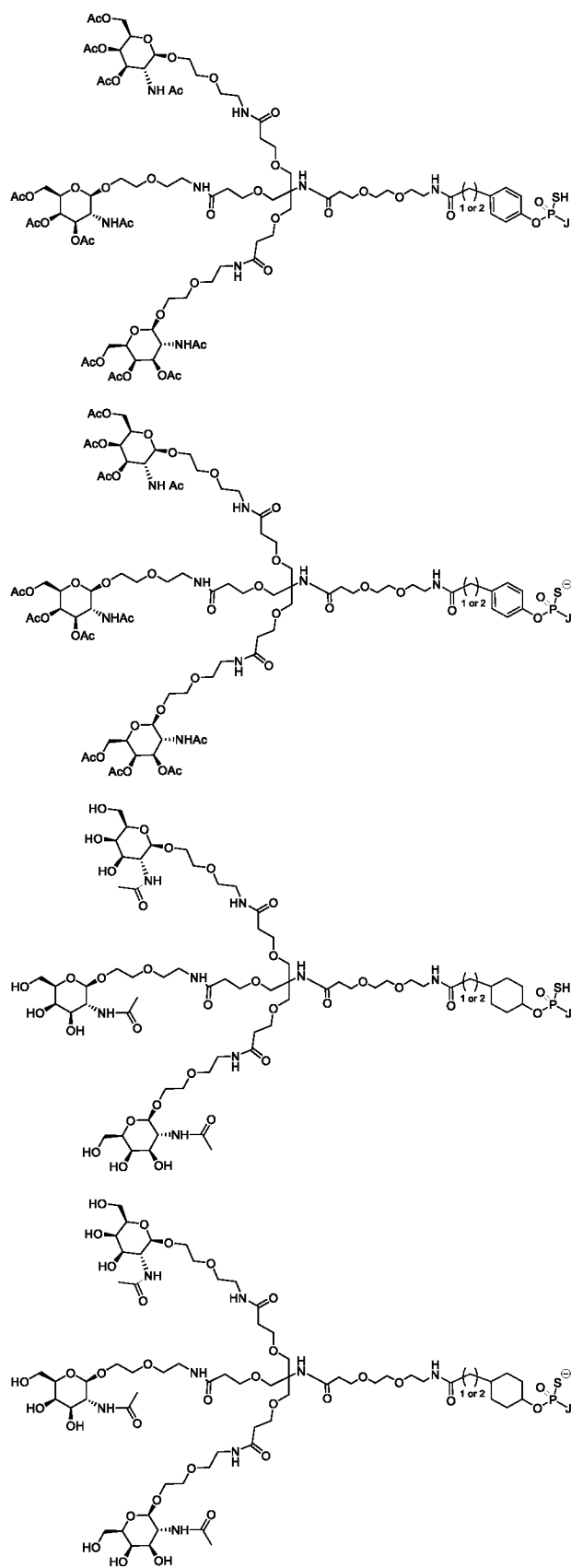


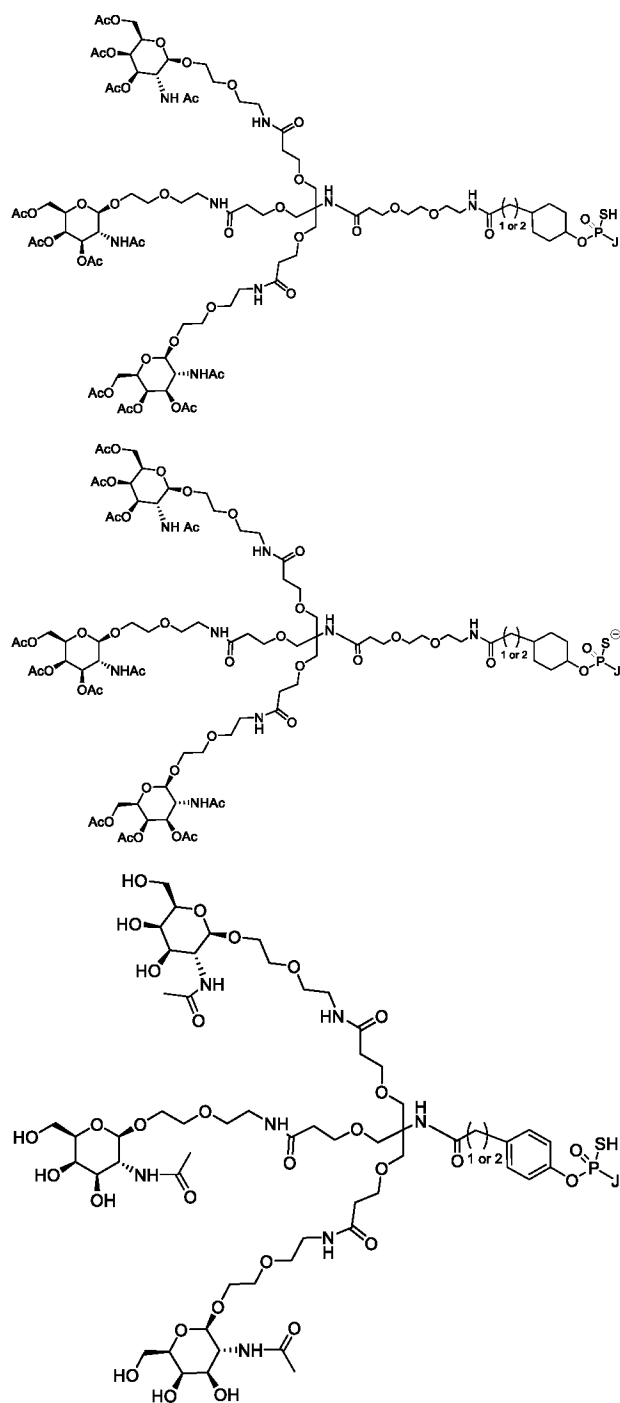


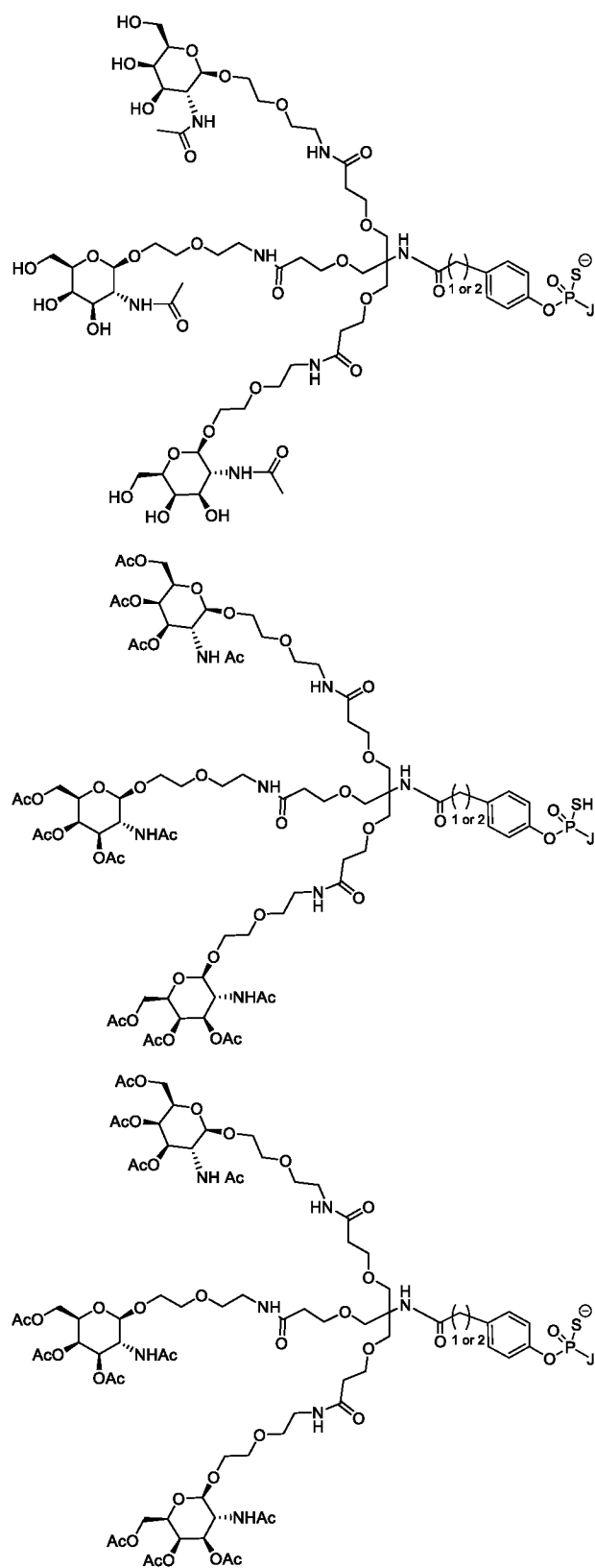


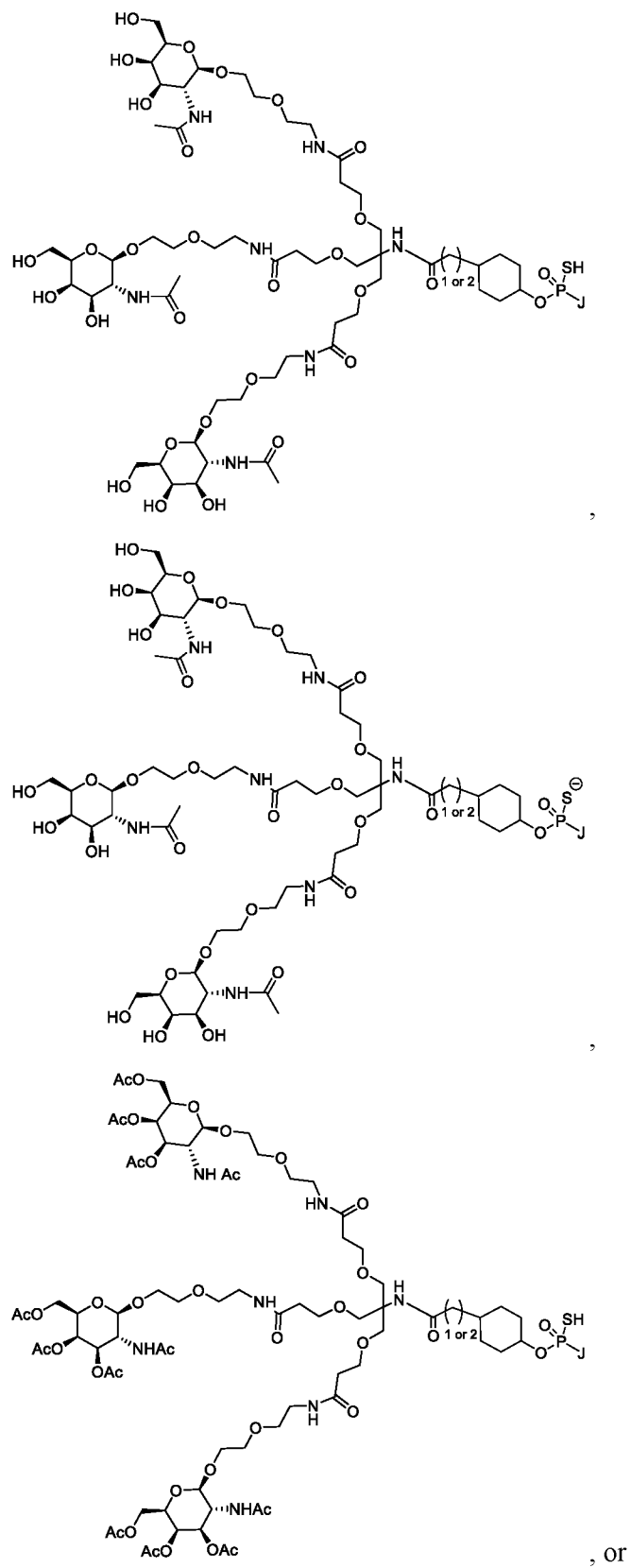


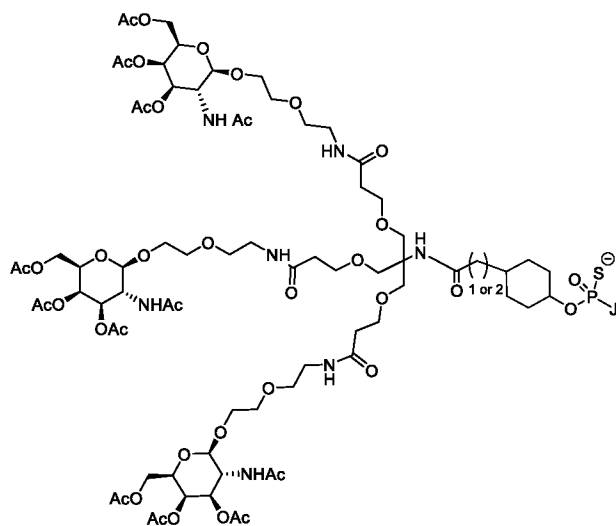






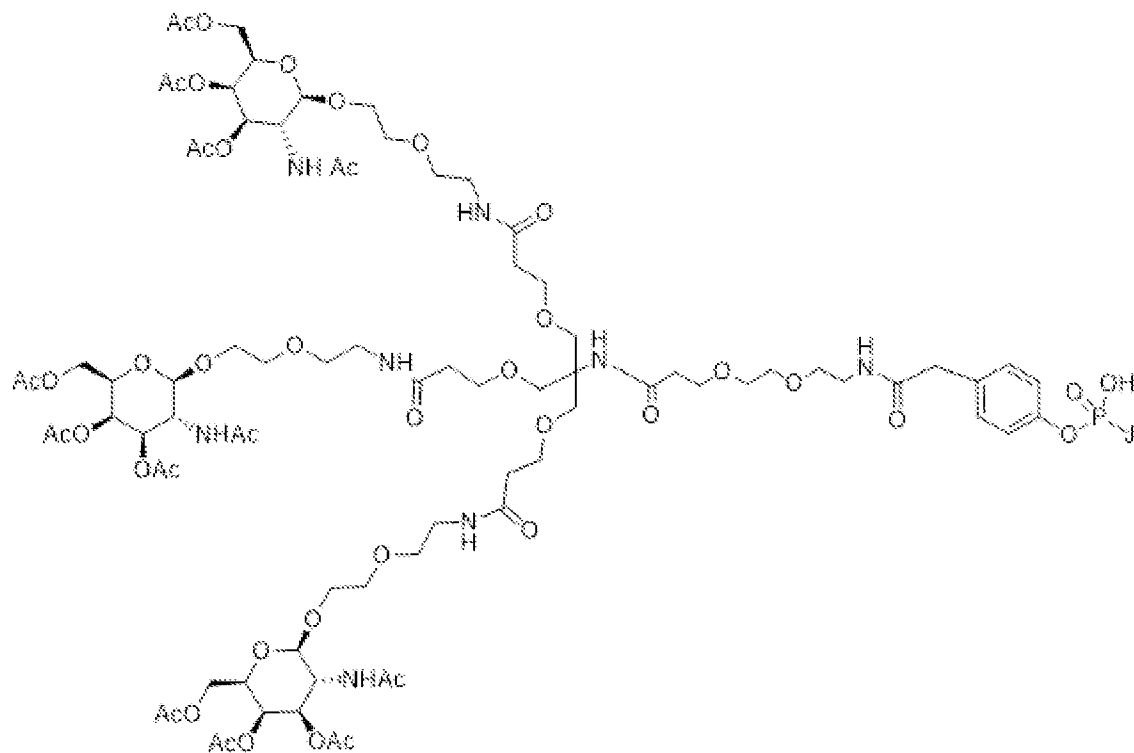






[0097] In some embodiments, the oligonucleotide (J) is attached at a 5' end or a 3' end of the oligonucleotide. In some embodiments, the oligonucleotide comprises DNA. In some embodiments, the oligonucleotide comprises RNA. In some embodiments, the oligonucleotide comprises one or more modified internucleoside linkages. In some embodiments, the one or more modified internucleoside linkages comprise alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, 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. In some embodiments, the compound binds to an asialoglycoprotein receptor. In some embodiments, the compound targets a hepatocyte.

[0098] Some embodiments include the following, where J is the oligonucleotide:

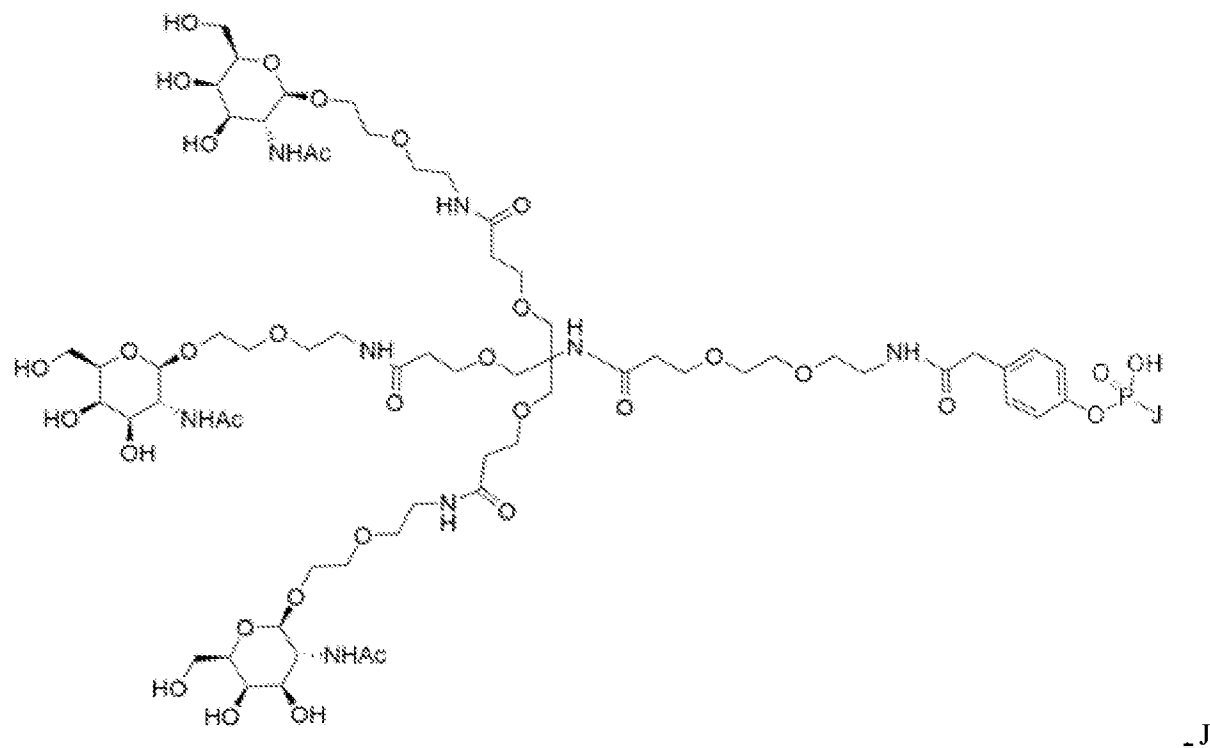


J may

include one or more additional phosphates, or one or more phosphorothioates linking to the

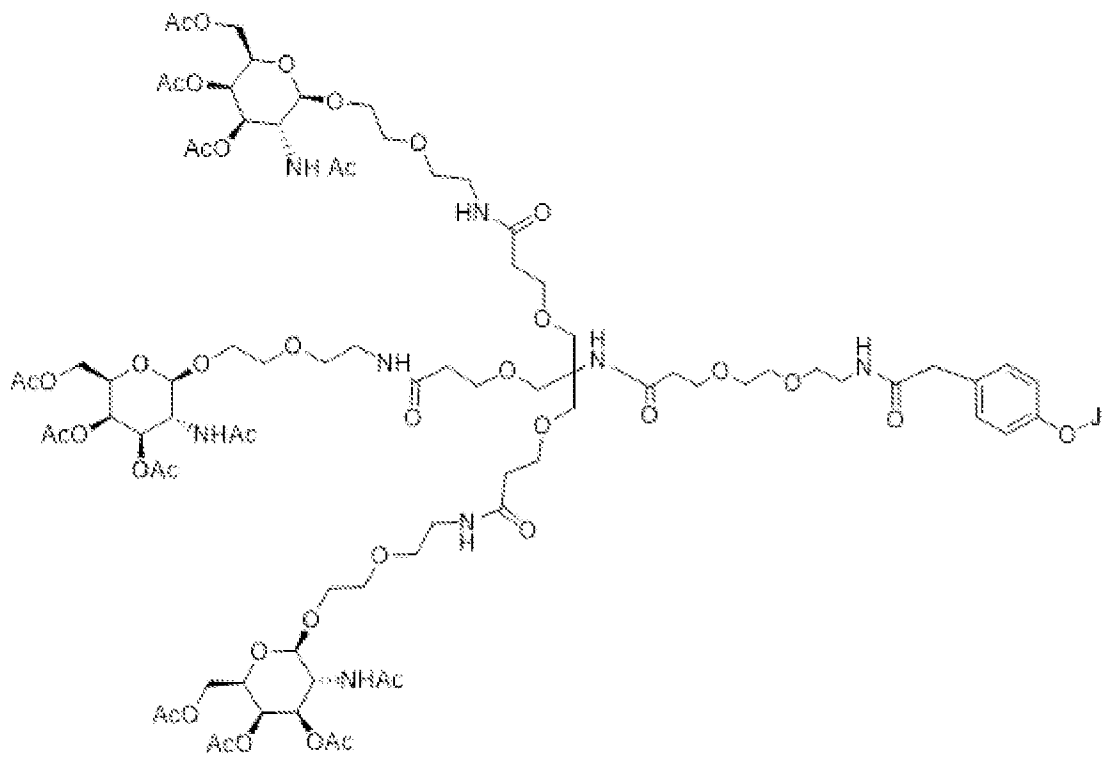
oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[0099] Some embodiments include the following, where J is the oligonucleotide:



may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

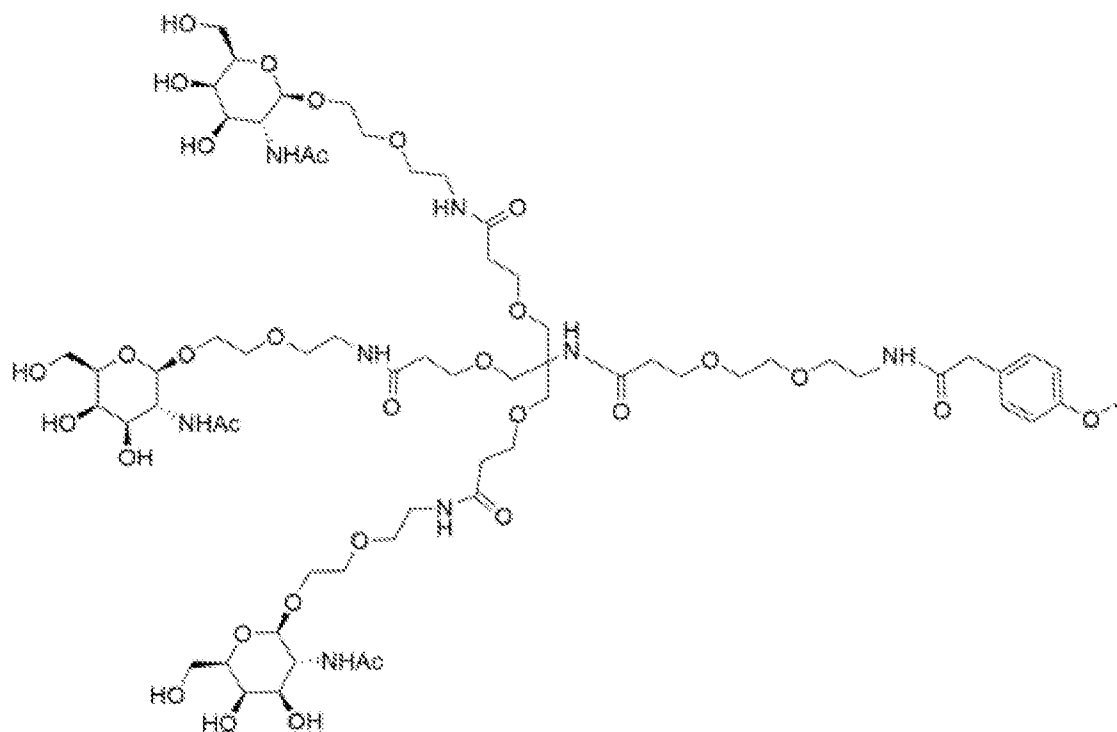
[00100] Some embodiments include the following, where J is the oligonucleotide:



J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or

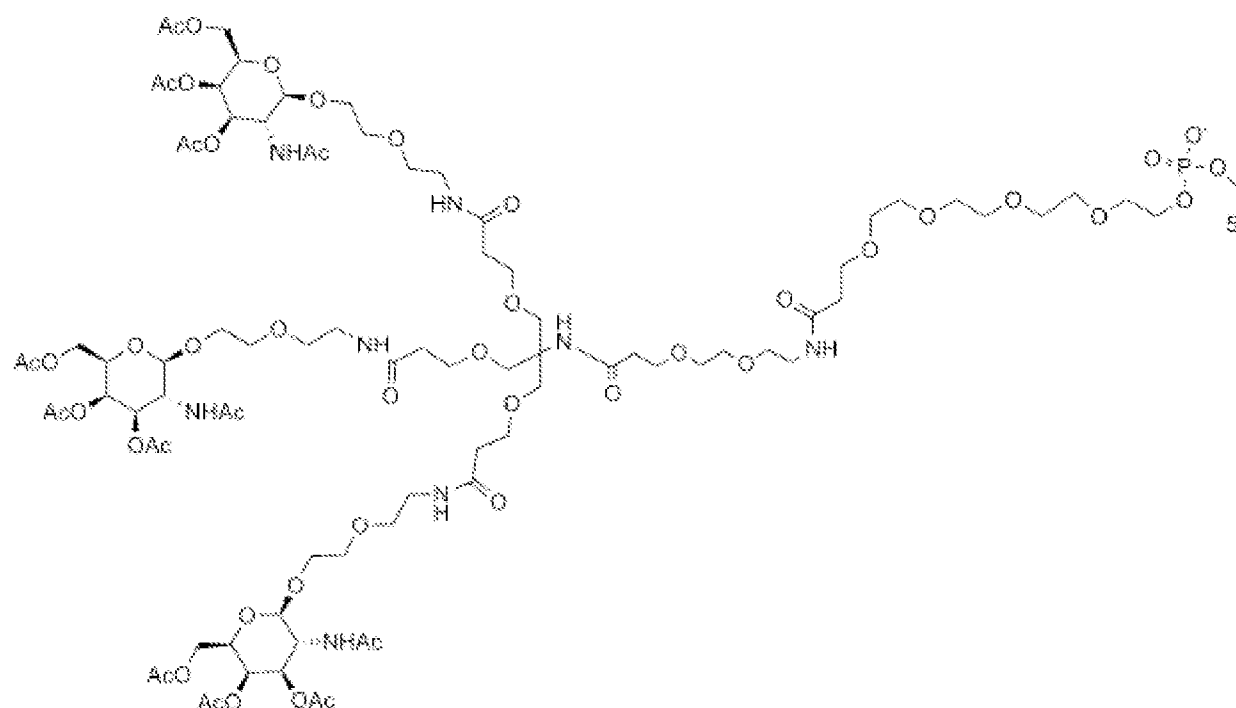
more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[00101] Some embodiments include the following, where J is the oligonucleotide:

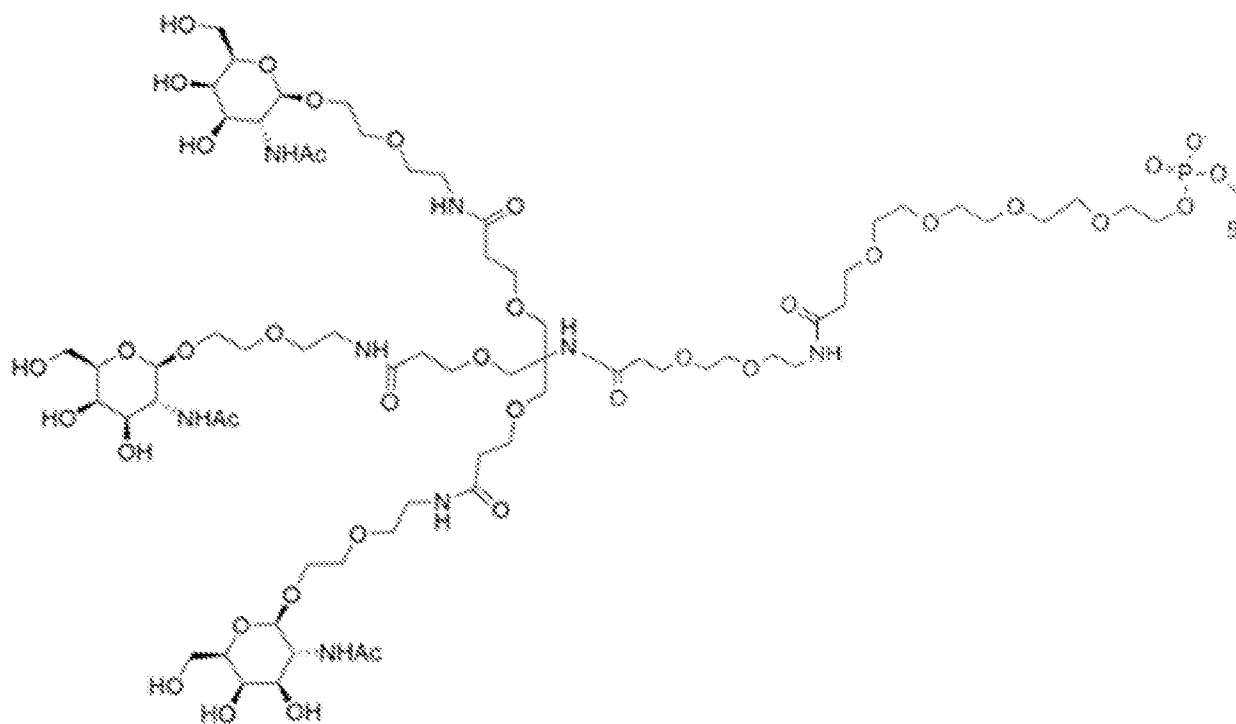


. The structure in this compound attached to the oligonucleotide (J) may be referred to as “ETL17,” and is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

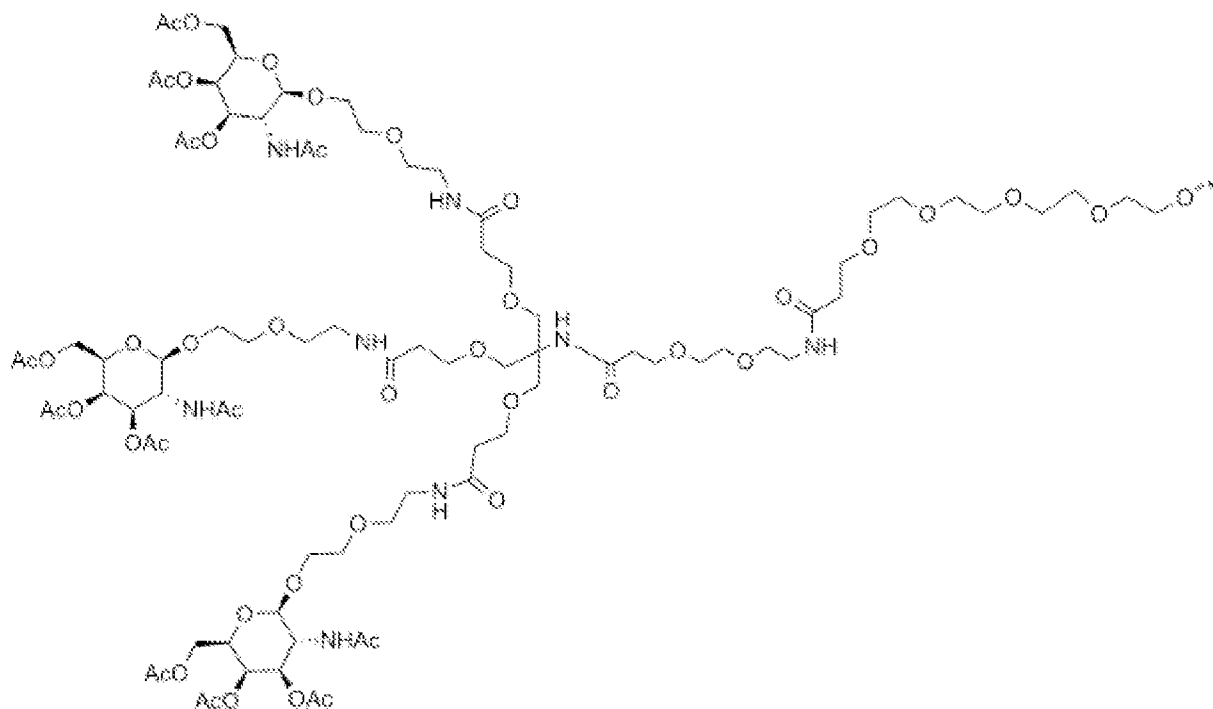
[00102] Some embodiments include the following, where the phosphate or “5’” indicates a connection to the oligonucleotide:



[00103] Some embodiments include the following, where the phosphate or “5” indicates a connection to the oligonucleotide:

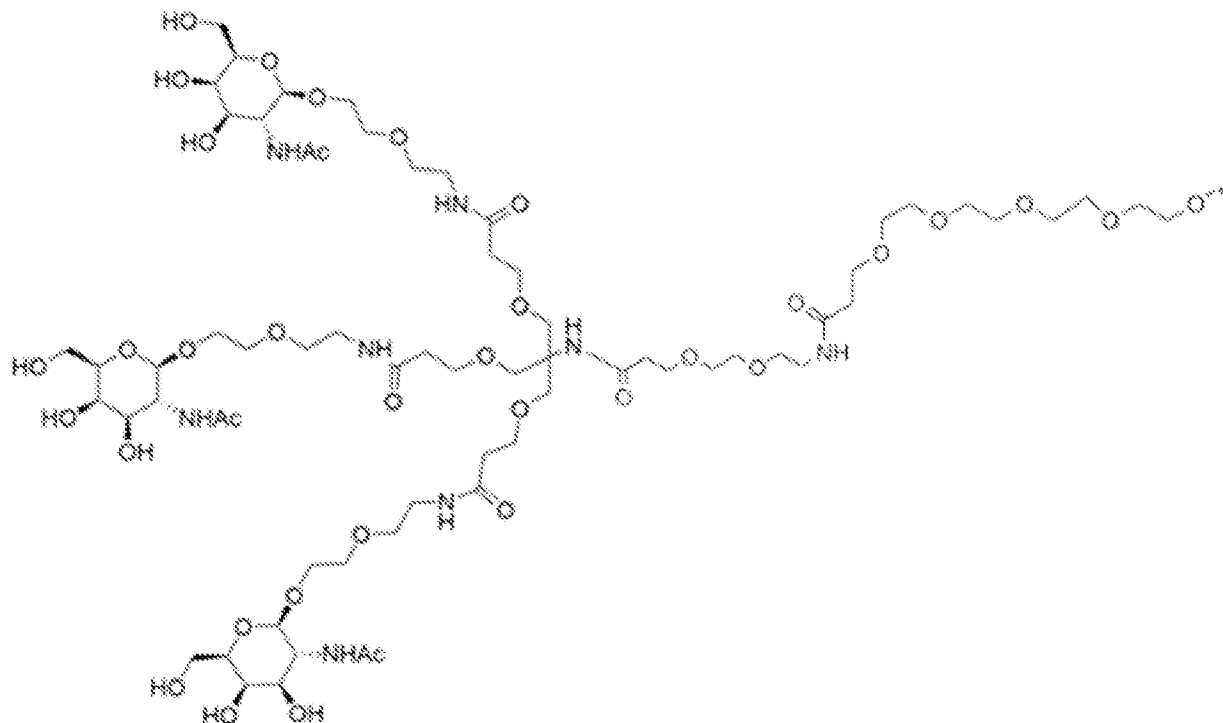


[00104] Some embodiments include the following, where J is the oligonucleotide:



include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[00105] Some embodiments include the following, where J is the oligonucleotide:



The structure in this compound attached to the oligonucleotide (J) may be referred to as “ETL1,” and is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a

phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

3. *siRNA modification patterns*

[00106] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises modification pattern 1S:

5'-NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9819), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 2S:

5'-nsnsnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9820), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 3S: 5'-nsnsnnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9821), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 4S: 5'-NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsnN-moiety-3' (SEQ ID NO: 9822), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 5S: 5'-nsnsnnNfnNfnNfnNfnNfnNfnNfsnsnN-moiety-3' (SEQ ID NO: 9823), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the moiety in modification pattern 4S or 5S includes an integrin targeting ligand. In some embodiments, the moiety in modification pattern 4S or 5S is a sugar moiety. In some embodiments, the sense strand comprises modification pattern 6S: 5'-NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9824), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 7S: 5'-nsnsnnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9825), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 8S: 5'-nsnsnnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9826), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 9S: 5'-nsnsnnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9827), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00107] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises modification pattern 1AS:

5'-nsNfsnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 9828), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some

embodiments, the antisense strand comprises modification pattern 2AS:

5'-nsNfsnnnnNfnNfNfnnnnnNfnNfnnnnsnsn-3' (SEQ ID NO: 9829), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 3AS:

5'-nsNfsnnnnNfnnnnnnnNfnNfnnnnsnsn-3' (SEQ ID NO: 9830), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 4AS:

5'-nsNfsnNfnNfnnnnnnnNfnNfnnnnsnsn-3' (SEQ ID NO: 9831), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 5AS:

5'-nsNfsnnnnnnnnnnNfnNfnnnnsnsn-3' (SEQ ID NO: 9832), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 6AS:

5'-nsNfsnnnnNfnNfnnnnnNfnNfnnnnsnsn-3' (SEQ ID NO: 9833), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 7AS:

5'-nsNfsnNfnNfnNfnNfnNfnNfnNfnnsnsn-3' (SEQ ID NO: 9834), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 8AS:

5'-nsNfsnnnnnnnnnnNfnnnnsnsn-3' (SEQ ID NO: 9835), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00108] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises pattern 1S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 2S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 3S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 4S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 5S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 6S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 7S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 8S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the sense strand comprises pattern 9S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS.

[00109]In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 1AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 2AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 3AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 4AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 5AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 6AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 7AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S and the antisense strand comprises pattern 8AS.

[00110]In some embodiments, the sense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, or 8AS. In some embodiments, the antisense strand comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, or 9S. In some embodiments, the sense strand or the antisense strand comprises modification pattern ASO1.

[00111]In some embodiments, purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, purines of the sense strand comprise 2' -O-methyl modified purines. In some embodiments, purines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified purines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the sense strand comprise 2' -O-methyl modified purines. In some embodiments, all purines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified purines.

[00112]In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise 2' -O-methyl modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' -O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified pyrimidines.

[00113]In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' -O-methyl modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise 2' -O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' -O-methyl modified purines, and pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, purines of the sense strand comprise a mixture of 2' fluoro and 2' -O-methyl modified

purines. In some embodiments, pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and purines of the sense strand comprise 2' fluoro modified purines.

[00114]In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the sense strand comprise 2' fluoro modified purines.

[00115]In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines.

[00116]In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[00117]In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified

purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines, and pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and purines of the antisense strand comprise 2' fluoro modified purines.

[00118] In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the antisense strand comprise 2' fluoro modified purines.

[00119] Disclosed herein, in some embodiments, are modified oligonucleotides. The modified oligonucleotide may be an siRNA that includes modifications to the ribose rings, and phosphate linkages. The modifications may be in particular patterns that maximize cell delivery, stability, and efficiency. The siRNA may also include a vinyl phosphonate and a hydrophobic group. These modifications may aid in delivery to a cell or tissue within a subject. The modified oligonucleotide may be used in a method such as a treatment method or a method of reducing gene expression.

[00120] In some embodiments, the oligonucleotide comprises a duplex consisting of 21 nucleotide single strands with base pairing between 19 of the base pairs. In some embodiments, the duplex comprises single-stranded 2 nucleotide overhangs at the 3' ends of each strand. One strand (antisense strand) is complementary to a MST1R mRNA. Each end of the antisense strand has one to two phosphorothioate

bonds. The 5' end has an optional phosphate mimic such as a vinyl phosphonate. In some embodiments, the oligonucleotide is used to knock down a MST1R mRNA or a target protein. In some embodiments, the sense strand has the same sequence as the MST1R mRNA. In some embodiments, there are 1-2 phosphorothioates at the 3' end. In some embodiments, there are 1 or no phosphorothioates at the 5' end. In some embodiments, there is a hydrophobic conjugate of 12 to 25 carbons attached at the 5' end via a phosphodiester bond.

[00121] In some cases, the sense strand of any of the siRNAs comprises siRNA with a particular modification pattern. In some embodiments of the modification pattern, position 9 counting from the 5' end of the sense strand may have a 2'F modification. In some embodiments, when position 9 of the sense strand is a pyrimidine, then all purines in the sense strand have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense strand, then position 9 is the only position with a 2'F modification in the sense strand. In some embodiments, when position 9 and only one other base between positions 5 and 11 of the sense strand are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in the sense strand. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of the sense strand are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of the sense strand, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to any or all of these sense strand rules.

[00122] In some embodiments, when position 9 of the sense strand is a purine, then all purines in the sense strand have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense strand, then position 9 is the only position with a 2'F modification in the sense strand. In some embodiments, when position 9 and only one other base between positions 5 and 11 of the sense strand are purines, then both of these purines are the only two positions with a 2'F modification in the sense strand. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of the sense strand are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of the sense strand, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to any or all of these sense strand rules.

[00123] In some cases, position 9 of the sense strand can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of the sense strand. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to these sense strand rules.

[00125]In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 9**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 9**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 9**. The siRNA may include the same internucleoside linkage modifications or nucleoside modifications as those in **Table 9**. The siRNA may include any different internucleoside linkage modifications or nucleoside modifications different from those in **Table 9**. The siRNA may include some unmodified internucleoside linkages or nucleosides.

[00126] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 10**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 10**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 10**. The siRNA may include the same internucleoside linkage modifications or nucleoside modifications as those in **Table 10**. The siRNA may include any different internucleoside linkage modifications or nucleoside modifications different from those in **Table 10**. The siRNA may include some unmodified internucleoside linkages or nucleosides.

[00127]In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO comprises modification pattern ASO1:

D. Formulations

[00129] In some embodiments, the pharmaceutically acceptable carrier comprises water. In some embodiments, the pharmaceutically acceptable carrier comprises a buffer. In some embodiments, the pharmaceutically acceptable carrier comprises a saline solution. In some embodiments, the pharmaceutically acceptable carrier comprises water, a buffer, or a saline solution. In some embodiments, the composition comprises a liposome. In some embodiments, the pharmaceutically acceptable carrier comprises liposomes, lipids, nanoparticles, proteins, protein-antibody complexes, peptides, cellulose,

nanogel, or a combination thereof. In some embodiments, the oligonucleotide is combined with lipids, nanoparticles, polymers, liposomes, micelles, or another delivery system.

[00130] In some embodiments, the composition is formulated for delivery to a subject's lungs. In some embodiments, the composition is formulated for inhalation. In some embodiments, the composition is formulated for aerosolization. In some embodiments, the composition is formulated for administration by a nebulizer.

II. METHODS AND USES

[00131] Disclosed herein, in some embodiments, are methods of administering a composition described herein to a subject. Some embodiments relate to use of a composition described herein, such as administering the composition to a subject.

[00132] Some embodiments relate to a method of treating a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of treatment. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration treats the disorder in the subject. In some embodiments, the composition treats the disorder in the subject.

[00133] In some embodiments, the treatment comprises prevention, inhibition, or reversion of the disorder in the subject. Some embodiments relate to use of a composition described herein in the method of preventing, inhibiting, or reversing the disorder. Some embodiments relate to a method of preventing, inhibiting, or reversing a disorder in a subject in need thereof. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents, inhibits, or reverses the disorder in the subject. In some embodiments, the composition prevents, inhibits, or reverses the disorder in the subject.

[00134] Some embodiments relate to a method of preventing a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of preventing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents the disorder in the subject. In some embodiments, the composition prevents the disorder in the subject.

[00135] Some embodiments relate to a method of inhibiting a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of inhibiting the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration inhibits the disorder in the subject. In some embodiments, the composition inhibits the disorder in the subject.

[00136] Some embodiments relate to a method of reversing a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of reversing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration reverses the disorder in the subject. In some embodiments, the composition reverses the disorder in the subject.

[00137] In some embodiments, the administration is systemic. In some embodiments, the administration is intravenous. In some embodiments, the administration is by injection. In some embodiments, the administration is to a subject's lungs. In some embodiments, the administration is by inhalation. In some embodiments, the administration is performed using a nebulizer.

A. Disorders

[00138] Some embodiments of the methods described herein include treating a disorder in a subject in need thereof. In some embodiments, the disorder is a lung disorder. Non-limiting examples of lung disorders include chronic obstructive pulmonary disease (COPD), acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), cough, lung cancer, interstitial lung disease, or pulmonary fibrosis. The lung disorder may include an obstructive airway disorder such as COPD or asthma. In some embodiments, the lung disorder includes COPD. In some embodiments, the lung disorder includes acute exacerbation of COPD. In some embodiments, the lung disorder includes emphysema. In some embodiments, the lung disorder includes chronic bronchitis. In some embodiments, the lung disorder includes asthma. In some embodiments, the lung disorder includes status asthmaticus. In some embodiments, the lung disorder includes ACOS. In some embodiments, the lung disorder includes cough. In some embodiments, the lung disorder includes lung cancer. In some embodiments, the lung disorder includes interstitial lung disease. In some embodiments, the lung disorder includes pulmonary fibrosis.

B. Subjects

[00139] Some embodiments of the methods described herein include treatment of a subject. Non-limiting examples of subjects include vertebrates, animals, mammals, dogs, cats, cattle, rodents, mice, rats, primates, monkeys, and humans. In some embodiments, the subject is a vertebrate. In some embodiments, the subject is an animal. In some embodiments, the subject is a mammal. In some embodiments, the subject is a dog. In some embodiments, the subject is a cat. In some embodiments, the subject is a cattle. In some embodiments, the subject is a mouse. In some embodiments, the subject is a rat. In some embodiments, the subject is a primate. In some embodiments, the subject is a monkey. In some embodiments, the subject is an animal, a mammal, a dog, a cat, cattle, a rodent, a mouse, a rat, a primate, or a monkey. In some embodiments, the subject is a human. In some embodiments, the subject is male. In some embodiments, the subject is female. In some embodiments, the subject is an adult (e.g. at least 18 years old).

C. Baseline measurements

[00140] Some embodiments of the methods described herein include obtaining a baseline measurement from a subject. For example, in some embodiments, a baseline measurement is obtained from the subject prior to treating the subject. Non-limiting examples of baseline measurements include a baseline lung function measurement, a baseline leukocyte measurement, a baseline chronic obstructive pulmonary disease (COPD) exacerbation measurement, a baseline asthma exacerbation measurement, a baseline MSTIR protein measurement, or a baseline *MSTIR* mRNA measurement.

[00141] In some embodiments, the baseline measurement is obtained directly from the subject. In some embodiments, the baseline measurement is obtained by observation, for example by observation of the subject or of the subject's tissue. In some embodiments, the baseline measurement is obtained noninvasively using an imaging device.

[00142] In some embodiments, the baseline measurement is obtained in a sample from the subject. In some embodiments, the baseline measurement is obtained in one or more histological tissue sections. In some embodiments, the baseline measurement is obtained by performing an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay, on the sample obtained from the subject. In some embodiments, the baseline measurement is obtained by an immunoassay, a colorimetric assay, a fluorescence assay, or a chromatography (e.g. HPLC) assay. In some embodiments, the baseline measurement is obtained by PCR.

[00143] In some embodiments, the baseline measurement is a baseline lung function measurement. In some embodiments, the baseline measurement is a baseline spirometry measurement. The baseline spirometry measurement may be obtained using a spirometer. The spirometer may generate a spirogram comprising a volume-time curve or a flow-volume loop. In some embodiments, the baseline spirometry measurement is obtained by having the subject breathe into a spirometer sensor. Examples of baseline spirometry measurements may include a baseline forced expiratory volume in 1 second (FEV1) measurement, a baseline forced expiratory volume in 1 second percent predicted (FEV1pp) measurement, a baseline forced vital capacity (FVC) measurement, a baseline FEV1/FVC ratio, a baseline forced expiratory volume, or a baseline peak expiratory flow measurement. In some embodiments, the baseline measurement includes a baseline forced expiratory volume in 1 second (FEV1) measurement. In some embodiments, the baseline measurement includes a baseline forced expiratory volume in 1 second percent predicted (FEV1pp) measurement. In some embodiments, the baseline measurement includes a baseline forced vital capacity (FVC) measurement. In some embodiments, the baseline measurement includes a baseline FEV1/FVC ratio. The baseline FEV1/FVC ratio may be below 70% or below 80%, in some cases. In some embodiments, the baseline measurement includes a baseline forced expiratory volume. In some embodiments, the baseline measurement includes a baseline peak expiratory flow measurement.

[00144] In some embodiments, the baseline measurement includes a baseline leukocyte measurement. In some embodiments, the baseline leukocyte measurement includes a baseline circulating leukocyte measurement. In some embodiments, the baseline leukocyte measurement includes a baseline lung tissue leukocyte measurement. In some embodiments, the baseline leukocyte measurement includes a baseline lung fluid (e.g. bronchoalveolar fluid) leukocyte measurement. In some embodiments, the baseline leukocyte measurement includes a baseline leukocyte count. In some embodiments, the baseline leukocyte measurement includes a baseline leukocyte concentration. In some embodiments, the baseline leukocyte measurement includes a baseline leukocyte percentage. The percentage may be in relation to other cells. Examples of leukocytes that may be included in the baseline leukocyte measurement include neutrophils, eosinophils, basophils, monocytes, or lymphocytes. The leukocytes may include neutrophils. The leukocytes may include eosinophils. The leukocytes may include basophils. The leukocytes may include

monocytes. The leukocytes may include lymphocytes. In some embodiments, the baseline leukocyte measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline leukocyte measurement is high, relative to a control leukocyte measurement. For example, a subject who has not been treated with a composition described herein and who has an inflammatory lung disorder may have a high leukocyte count in the subject's blood or lungs. In some embodiments, the baseline leukocyte measurement is determined in lung tissue or a lung fluid such as bronchoalveolar fluid, and may include a baseline measurement of neutrophils and macrophages.

[00145] In some embodiments, the baseline measurement includes a baseline chronic obstructive pulmonary disease (COPD) exacerbation measurement. A COPD exacerbation may include a COPD flare-up such as an acute increase in severity of a respiratory symptom such as difficulty breathing. The baseline COPD exacerbation measurement may include a baseline number of COPD flare-ups, and may be included in a given time frame such as flare-ups per day, week, month, or year. The baseline COPD exacerbation measurement may include a baseline frequency of COPD exacerbations. The baseline COPD exacerbation measurement may include a baseline measurement of worsening of a respiratory symptom, such as increased dyspnea, cough, sputum volume, or sputum purulence. The baseline COPD exacerbation measurement may include a baseline measurement of an event such as when a the subject's conditions change enough to require a change in treatment. The baseline COPD exacerbation measurement may include a baseline peak flow test, a baseline breath nitric oxide measurement, or a baseline blood oxygen level test.

[00146] In some embodiments, the baseline measurement includes a baseline asthma exacerbation measurement. An asthma exacerbation may include an asthma attack, for example narrowing of a bronchial tube that causes difficulty breathing. The baseline asthma exacerbation measurement may include a baseline number of number of asthma attacks, and may be included in a given time frame such as flare-ups per day, week, month, or year. The baseline asthma exacerbation measurement may include a baseline frequency of asthma exacerbations. The baseline asthma exacerbation measurement may include a baseline bronchial tube measurement such as a bronchial tube diameter, a bronchial tube circumference, or a bronchial tube area measurement. The baseline asthma exacerbation measurement may include a baseline amount of bronchial tube narrowing, such as a percent constriction. The baseline asthma exacerbation measurement may include a baseline wheezing measurement, a baseline coughing measurement, a baseline chest tightening measurement, a baseline shortness of breath measurement, a baseline agitation measurement, a baseline hyperventilation measurement, a baseline heart rate measurement, a baseline lung function measurement, or a baseline measurement of difficulty speaking or breathing. The baseline asthma exacerbation measurement may include a baseline peak flow test, a baseline breath nitric oxide measurement, or a baseline blood oxygen level test.

[00147] In some embodiments, the baseline measurement is a baseline MST1R protein measurement. In some embodiments, the baseline MST1R protein measurement comprises a baseline MST1R protein level. In some embodiments, the baseline MST1R protein level is indicated as a mass or percentage of MST1R protein per sample weight. In some embodiments, the baseline MST1R protein level is indicated as a mass

or percentage of *MST1R* protein per sample volume. In some embodiments, the baseline *MST1R* protein level is indicated as a mass or percentage of *MST1R* protein per total protein within the sample. In some embodiments, the baseline *MST1R* protein measurement is a baseline lung *MST1R* protein measurement. In some embodiments, the baseline *MST1R* protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[00148] In some embodiments, the baseline measurement is a baseline *MST1R* mRNA measurement. In some embodiments, the baseline *MST1R* mRNA measurement comprises a baseline *MST1R* mRNA level. In some embodiments, the baseline *MST1R* mRNA level is indicated as an amount or percentage of *MST1R* mRNA per sample weight. In some embodiments, the baseline *MST1R* mRNA level is indicated as an amount or percentage of *MST1R* mRNA per sample volume. In some embodiments, the baseline *MST1R* mRNA level is indicated as an amount or percentage of *MST1R* mRNA per total mRNA within the sample. In some embodiments, the baseline *MST1R* mRNA level is indicated as an amount or percentage of *MST1R* mRNA per total nucleic acids within the sample. In some embodiments, the baseline *MST1R* mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the baseline *MST1R* mRNA measurement is obtained by an assay such as a polymerase chain reaction (PCR) assay. In some embodiments, the PCR comprises quantitative PCR (qPCR). In some embodiments, the PCR comprises reverse transcription of the *MST1R* mRNA.

[00149] Some embodiments of the methods described herein include obtaining a sample from a subject. In some embodiments, the baseline measurement is obtained in a sample obtained from the subject. In some embodiments, the sample is obtained from the subject prior to administration or treatment of the subject with a composition described herein. In some embodiments, a baseline measurement is obtained in a sample obtained from the subject prior to administering the composition to the subject.

[00150] In some embodiments, the sample comprises a fluid. In some embodiments, the sample is a fluid sample. For example, a fluid sample may be used in obtaining a leukocyte measurement or baseline measurement. In some embodiments, the sample is a blood, plasma, or serum sample. In some embodiments, the baseline *MST1R* mRNA measurement is obtained in a fluid sample. In some embodiments, the sample comprises blood. In some embodiments, the sample is a blood sample. In some embodiments, the sample is a whole-blood sample. In some embodiments, the blood is fractionated or centrifuged. In some embodiments, the sample comprises plasma. In some embodiments, the sample is a plasma sample. A blood sample may be a plasma sample. In some embodiments, the sample comprises serum. In some embodiments, the sample is a serum sample. A blood sample may be a serum sample. In some embodiments, the fluid sample includes a lung fluid sample. In some embodiments, the lung fluid sample includes alveolar fluid. In some embodiments, the lung fluid sample includes bronchial fluid. In some embodiments, the lung fluid sample includes bronchoalveolar fluid. The lung fluid may be obtained via a lavage method such as a bronchoalveolar lavage method. The lavage method may include the use of a bronchoscope.

[00151] In some embodiments, the sample comprises a tissue. In some embodiments, the sample is a tissue sample. In some embodiments, the tissue comprises lung, or vascular tissue. For example, the baseline *MST1R* mRNA measurement, or the baseline *MST1R* protein measurement, may be obtained in a lung sample obtained from the patient. In some embodiments, the tissue comprises lung tissue. The lung may include lung epithelial cells, type I alveolar cells, type II alveolar cells, macrophages, alveolar macrophages, goblet cells, club cells, or fibroblasts. In some embodiments, the tissue comprises vascular tissue. The vascular tissue may include vascular endothelial cells. For example, the lung tissue may include vascular endothelial cells.

[00152] In some embodiments, the sample includes cells. In some embodiments, the sample comprises a cell. In some embodiments, the cell is a lung cell. In some embodiments, the lung cell is a lung epithelial cell. In some embodiments, the lung cell is a type I alveolar cell. In some embodiments, the lung cell is a type II alveolar cell. In some embodiments, the lung cell is a macrophage. In some embodiments, the lung cell is an alveolar macrophage. In some embodiments, the lung cell is a goblet cell. In some embodiments, the lung cell is a club cell. In some embodiments, the lung cell is a fibroblast. In some embodiments, the cell is a vasculature cell. In some embodiments, the vasculature cell is an endothelial cell.

D. Effects

[00153] In some embodiments, the composition or administration of the composition affects a measurement such as a lung function measurement, a leukocyte measurement, a chronic obstructive pulmonary disease (COPD) exacerbation measurement, an asthma exacerbation measurement, a *MST1R* protein measurement (for example, lung *MST1R* protein levels), or a *MST1R* mRNA measurement, relative to the baseline measurement.

[00154] Some embodiments of the methods described herein include obtaining the measurement from a subject. For example, the measurement may be obtained from the subject after treating the subject. In some embodiments, the measurement is obtained in a second sample (such as a fluid or tissue sample described herein) obtained from the subject after the composition is administered to the subject. In some embodiments, the measurement is an indication that the disorder has been treated.

[00155] In some embodiments, the measurement is obtained directly from the subject. In some embodiments, the measurement is obtained noninvasively using an imaging device. In some embodiments, the measurement is obtained in a second sample from the subject. In some embodiments, the measurement is obtained in one or more histological tissue sections. In some embodiments, the measurement is obtained by performing an assay on the second sample obtained from the subject. In some embodiments, the measurement is obtained by an assay, such as an assay described herein. In some embodiments, the assay is an immunoassay, a colorimetric assay, a fluorescence assay, a chromatography (e.g. HPLC) assay, or a PCR assay. In some embodiments, the measurement is obtained by an assay such as an immunoassay, a colorimetric assay, a fluorescence assay, or a chromatography (e.g. HPLC) assay. In some embodiments, the measurement is obtained by PCR. In some embodiments, the measurement is obtained by histology. In some embodiments, the measurement is obtained by observation. In some embodiments, additional measurements are made, such as in a 3rd sample, a 4th sample, or a fifth sample.

[00156]In some embodiments, the measurement is obtained within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, within 6 hours, within 12 hours, within 18 hours, or within 24 hours after the administration of the composition. In some embodiments, the measurement is obtained within 1 day, within 2 days, within 3 days, within 4 days, within 5 days, within 6 days, or within 7 days after the administration of the composition. In some embodiments, the measurement is obtained within 1 week, within 2 weeks, within 3 weeks, within 1 month, within 2 months, within 3 months, within 6 months, within 1 year, within 2 years, within 3 years, within 4 years, or within 5 years after the administration of the composition. In some embodiments, the measurement is obtained after 1 hour, after 2 hours, after 3 hours, after 4 hours, after 5 hours, after 6 hours, after 12 hours, after 18 hours, or after 24 hours after the administration of the composition. In some embodiments, the measurement is obtained after 1 day, after 2 days, after 3 days, after 4 days, after 5 days, after 6 days, or after 7 days after the administration of the composition. In some embodiments, the measurement is obtained after 1 week, after 2 weeks, after 3 weeks, after 1 month, after 2 months, after 3 months, after 6 months, after 1 year, after 2 years, after 3 years, after 4 years, or after 5 years, following the administration of the composition.

[00157]In some embodiments, the composition reduces the measurement relative to the baseline measurement. For example, an adverse phenotype of a lung disorder may be reduced upon administration of the composition. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline measurement. In some embodiments, the measurement is decreased by about 10% or more, relative to the baseline measurement. In some embodiments, the measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline measurement. In some embodiments, the measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline measurement. In some embodiments, the measurement is decreased by no more than about 10%, relative to the baseline measurement. In some embodiments, the measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline measurement. In some embodiments, the measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00158]In some embodiments, the composition increases the measurement relative to the baseline measurement. For example, a protective lung phenotype may be increased upon administration of the composition. In some embodiments, the increase is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the increase is measured directly in the subject after administering the composition to the subject. In some embodiments, the measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to

the baseline measurement. In some embodiments, the measurement is increased by about 10% or more, relative to the baseline measurement. In some embodiments, the measurement is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline measurement. In some embodiments, the measurement is increased by about 100% or more, increased by about 250% or more, increased by about 500% or more, increased by about 750% or more, or increased by about 1000% or more, relative to the baseline measurement. In some embodiments, the measurement is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline measurement. In some embodiments, the measurement is increased by no more than about 10%, relative to the baseline measurement. In some embodiments, the measurement is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline measurement. In some embodiments, the measurement is increased by no more than about 100%, increased by no more than about 250%, increased by no more than about 500%, increased by no more than about 750%, or increased by no more than about 1000%, relative to the baseline measurement. In some embodiments, the measurement is increased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 250%, 500%, 750%, or 1000%, or by a range defined by any of the two aforementioned percentages.

[00159] In some embodiments, the measurement is a lung function measurement. In some embodiments, the measurement is a spirometry measurement. The spirometry measurement may be obtained using a spirometer. The spirometer may generate a spirogram comprising a volume-time curve or a flow-volume loop. In some embodiments, the spirometry measurement is obtained by having the subject breathe into a spirometer sensor. Examples of spirometry measurements may include 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, a forced expiratory volume, or a peak expiratory flow measurement. In some embodiments, the measurement includes a forced expiratory volume in 1 second (FEV1) measurement. In some embodiments, the measurement includes a forced expiratory volume in 1 second percent predicted (FEV1pp) measurement. In some embodiments, the measurement includes a forced vital capacity (FVC) measurement. In some embodiments, the measurement includes a FEV1/FVC ratio. The FEV1/FVC ratio may be below 70% or below 80%, in some cases. In some embodiments, the measurement includes a forced expiratory volume. In some embodiments, the measurement includes a peak expiratory flow measurement.

[00160] In some embodiments, the composition increases the lung function measurement relative to the baseline lung function measurement. In some embodiments, the increase is measured directly in the subject after administering the composition to the subject. In some embodiments, the lung function measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by about 10% or more, relative to the baseline lung function measurement. In some

embodiments, the lung function measurement is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by about 100% or more, increased by about 250% or more, increased by about 500% or more, increased by about 750% or more, or increased by about 1000% or more, relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by no more than about 10%, relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by no more than about 100%, increased by no more than about 250%, increased by no more than about 500%, increased by no more than about 750%, or increased by no more than about 1000%, relative to the baseline lung function measurement. In some embodiments, the lung function measurement is increased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 250%, 500%, 750%, or 1000%, or by a range defined by any of the two aforementioned percentages.

[00161] In some embodiments, the measurement includes a leukocyte measurement. In some embodiments, the leukocyte measurement includes a circulating leukocyte measurement. In some embodiments, the leukocyte measurement includes a lung tissue leukocyte measurement. In some embodiments, the leukocyte measurement includes a lung fluid (e.g. bronchoalveolar fluid) leukocyte measurement. In some embodiments, the leukocyte measurement includes a leukocyte count. In some embodiments, the leukocyte measurement includes a leukocyte concentration. In some embodiments, the leukocyte measurement includes a leukocyte percentage. The percentage may be in relation to other cells. Examples of leukocytes that may be included in the leukocyte measurement include neutrophils, eosinophils, basophils, monocytes, or lymphocytes. The leukocytes may include neutrophils. The leukocytes may include eosinophils. The leukocytes may include basophils. The leukocytes may include monocytes. The leukocytes may include lymphocytes. In some embodiments, the leukocyte measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the leukocyte measurement is normal, relative to a control leukocyte measurement. For example, a subject who has been treated with a composition described herein and who has an inflammatory lung disorder may have had a high leukocyte count that is now low or normal. In some embodiments, the leukocyte measurement is determined in lung tissue or a lung fluid such as bronchoalveolar fluid, and may include a measurement of neutrophils and macrophages.

[00162] In some embodiments, the composition reduces the leukocyte measurement relative to the baseline leukocyte measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the

leukocyte measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline leukocyte measurement. In some embodiments, the leukocyte measurement is decreased by about 10% or more, relative to the baseline leukocyte measurement. In some embodiments, the leukocyte measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, or about 80% or more, relative to the baseline leukocyte measurement. In some embodiments, the leukocyte measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline leukocyte measurement. In some embodiments, the leukocyte measurement is decreased by no more than about 10%, relative to the baseline leukocyte measurement. In some embodiments, the leukocyte measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, or no more than about 80%, relative to the baseline leukocyte measurement. In some embodiments, the leukocyte measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages. In some embodiments, the leukocyte measurement is increased by any of the aforementioned percentages or ranges of percentages, relative to the baseline leukocyte measurement.

[00163] In some embodiments, the measurement includes a chronic obstructive pulmonary disease (COPD) exacerbation measurement. A COPD exacerbation may include a COPD flare-up such as an acute increase in severity of a respiratory symptom such as difficulty breathing. The COPD exacerbation measurement may include a number of COPD flare-ups, and may be included in a given time frame such as flare-ups per day, week, month, or year. The COPD exacerbation measurement may include a frequency of COPD exacerbations. The COPD exacerbation measurement may include a measurement of worsening of a respiratory symptom, such as increased dyspnea, cough, sputum volume, or sputum purulence. The COPD exacerbation measurement may include a measurement of an event such as when a the subject's conditions change enough to require a change in treatment. The COPD exacerbation measurement may include a peak flow test, a breath nitric oxide measurement, or a blood oxygen level test.

[00164] In some embodiments, the composition reduces the COPD exacerbation measurement relative to the baseline COPD exacerbation measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the COPD exacerbation measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline COPD exacerbation measurement. In some embodiments, the COPD exacerbation measurement is decreased by about 10% or more, relative to the baseline COPD exacerbation measurement. In some embodiments, the COPD exacerbation measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline COPD exacerbation measurement. In some embodiments, the COPD exacerbation measurement

is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline COPD exacerbation measurement. In some embodiments, the COPD exacerbation measurement is decreased by no more than about 10%, relative to the baseline COPD exacerbation measurement. In some embodiments, the COPD exacerbation measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline COPD exacerbation measurement. In some embodiments, the COPD exacerbation measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00165] In some embodiments, the measurement includes an asthma exacerbation measurement. An asthma exacerbation may include an asthma attack, for example narrowing of a bronchial tube that causes difficulty breathing. The asthma exacerbation measurement may include a number of number of asthma attacks, and may be included in a given time frame such as flare-ups per day, week, month, or year. The asthma exacerbation measurement may include a frequency of asthma exacerbations. The asthma exacerbation measurement may include a bronchial tube measurement such as a bronchial tube diameter, a bronchial tube circumference, or a bronchial tube area measurement. The asthma exacerbation measurement may include an amount of bronchial tube narrowing, such as a percent constriction. The asthma exacerbation measurement may include a wheezing measurement, a coughing measurement, a chest tightening measurement, a shortness of breath measurement, a agitation measurement, a hyperventilation measurement, a heart rate measurement, a lung function measurement, or a measurement of difficulty speaking or breathing. The asthma exacerbation measurement may include a peak flow test, a breath nitric oxide measurement, or a blood oxygen level test.

[00166] In some embodiments, the composition reduces the asthma exacerbation measurement relative to the baseline asthma exacerbation measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the asthma exacerbation measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline asthma exacerbation measurement. In some embodiments, the asthma exacerbation measurement is decreased by about 10% or more, relative to the baseline asthma exacerbation measurement. In some embodiments, the asthma exacerbation measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline asthma exacerbation measurement. In some embodiments, the asthma exacerbation measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline asthma exacerbation measurement. In some embodiments, the asthma exacerbation measurement is decreased by no more than about 10%, relative to the baseline asthma exacerbation measurement. In some embodiments, the asthma exacerbation measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no

more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline asthma exacerbation measurement. In some embodiments, the asthma exacerbation measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00167] In some embodiments, the measurement is an *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement comprises an *MST1R* protein level. In some embodiments, the *MST1R* protein level is indicated as a mass or percentage of *MST1R* protein per sample weight. In some embodiments, the *MST1R* protein level is indicated as a mass or percentage of *MST1R* protein per sample volume. In some embodiments, the *MST1R* protein level is indicated as a mass or percentage of *MST1R* protein per total protein within the sample. In some embodiments, the *MST1R* protein measurement is a lung *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[00168] In some embodiments, the composition reduces the *MST1R* protein measurement relative to the baseline *MST1R* protein measurement. In some embodiments, the composition reduces tissue *MST1R* protein levels relative to the baseline *MST1R* protein measurement. In some embodiments, the composition reduces lung *MST1R* protein levels relative to the baseline *MST1R* protein measurement. In some embodiments, the reduced *MST1R* protein levels are measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the second sample is a lung sample. In some embodiments, the *MST1R* protein measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is decreased by about 10% or more, relative to the baseline *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is decreased by no more than about 10%, relative to the baseline *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline *MST1R* protein measurement. In some embodiments, the *MST1R* protein measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00169] In some embodiments, the measurement is an *MST1R* mRNA measurement. In some embodiments, the *MST1R* mRNA measurement comprises an *MST1R* mRNA level. In some embodiments, the *MST1R* mRNA level is indicated as an amount or percentage of *MST1R* mRNA per

sample weight. In some embodiments, the *MSTIR* mRNA level is indicated as an amount or percentage of *MSTIR* mRNA per sample volume. In some embodiments, the *MSTIR* mRNA level is indicated as an amount or percentage of *MSTIR* mRNA per total mRNA within the sample. In some embodiments, the *MSTIR* mRNA level is indicated as an amount or percentage of *MSTIR* mRNA per total nucleic acids within the sample. In some embodiments, the *MSTIR* mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the *MSTIR* mRNA measurement is obtained by an assay such as a PCR assay. In some embodiments, the PCR comprises qPCR. In some embodiments, the PCR comprises reverse transcription of the *MSTIR* mRNA.

[00170] In some embodiments, the composition reduces the *MSTIR* mRNA measurement relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is obtained in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the composition reduces *MSTIR* mRNA levels relative to the baseline *MSTIR* mRNA levels. In some embodiments, the reduced *MSTIR* mRNA levels are measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the second sample is a lung sample. In some embodiments, the *MSTIR* mRNA measurement is reduced by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is decreased by about 10% or more, relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is decreased by no more than about 10%, relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, relative to the baseline *MSTIR* mRNA measurement. In some embodiments, the *MSTIR* mRNA measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% or by a range defined by any of the two aforementioned percentages.

III. DEFINITIONS

[00171] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[00172] Throughout this application, various embodiments may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[00173] As used in the specification and claims, the singular forms “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a sample” includes a plurality of samples, including mixtures thereof.

[00174] The terms “determining,” “measuring,” “evaluating,” “assessing,” “assaying,” and “analyzing” are often used interchangeably herein to refer to forms of measurement. The terms include determining if an element is present or not (for example, detection). These terms can include quantitative, qualitative or quantitative and qualitative determinations. Assessing can be relative or absolute. “Detecting the presence of” can include determining the amount of something present in addition to determining whether it is present or absent depending on the context.

[00175] The terms “subject,” and “patient” may be used interchangeably herein. A “subject” can be a biological entity containing expressed genetic materials. The biological entity can be a plant, animal, or microorganism, including, for example, bacteria, viruses, fungi, and protozoa. The subject can be a mammal. The mammal can be a human. The subject may be diagnosed or suspected of being at high risk for a disease. In some cases, the subject is not necessarily diagnosed or suspected of being at high risk for the disease.

[00176] As used herein, the term “about” a number refers to that number plus or minus 10% of that number. The term “about” a range refers to that range minus 10% of its lowest value and plus 10% of its greatest value.

[00177] As used herein, the terms “treatment” or “treating” are used in reference to a pharmaceutical or other intervention regimen for obtaining beneficial or desired results in the recipient. Beneficial or desired results include but are not limited to a therapeutic benefit and/or a prophylactic benefit. A therapeutic benefit may refer to eradication or amelioration of symptoms or of an underlying disorder being treated. Also, a therapeutic benefit can be achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. A prophylactic effect includes delaying, preventing, or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. For prophylactic benefit, a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological

symptoms of a disease may undergo treatment, even though a diagnosis of this disease may not have been made.

[00178] The term “Cx-y” or “Cx-Cy” when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, the term “C1-6alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons.

[00179] The terms “Cx-yalkenyl” and “Cx-yalkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

[00180] The term “carbocycle” as used herein refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is carbon. Carbocycle includes 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. A bicyclic carbocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. A bicyclic carbocycle further includes spiro bicyclic rings such as spiro pentane. A bicyclic carbocycle includes any combination of ring sizes such as 3-3 spiro ring systems, 4-4 spiro ring systems, 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, naphthyl, and bicyclo[1.1.1]pentanyl.

[00181] The term “aryl” refers to an aromatic monocyclic or aromatic polycyclic hydrocarbon ring system. The aromatic monocyclic or aromatic polycyclic hydrocarbon ring system contains only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, i.e., it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene.

[00182] The term “cycloalkyl” refers to a saturated ring in which each atom of the ring is carbon. Cycloalkyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkyls include, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, spiro pentane, norbornyl (i.e., bicyclo[2.2.1]heptanyl), decalinyl, 7,7 dimethyl bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and the like.

[00183] The term “cycloalkenyl” refers to a saturated ring in which each atom of the ring is carbon and there is at least one double bond between two ring carbons. Cycloalkenyl may include monocyclic and

polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 5- to 12-membered bridged rings. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls include, e.g., cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

[00184] The term “halo” or, alternatively, “halogen” or “halide,” means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[00185] The term “haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2 trifluoroethyl, 1 chloromethyl 2 fluoroethyl, and the like. In some embodiments, the alkyl part of the haloalkyl radical is optionally further substituted as described herein.

[00186] The term “heterocycle” as used herein refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. A bicyclic heterocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, morpholine, piperidine or cyclohexene. A bicyclic heterocycle includes any combination of ring sizes such as 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. A bicyclic heterocycle further includes spiro bicyclic rings, e.g., 5 to 12-membered spiro bicycles, such as 2-oxa-6-azaspiro[3.3]heptane.

[00187] The term “heteroaryl” refers to a radical derived from a 5 to 18 membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is aromatic, i.e., it contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3 benzodioxolyl, benzofuranyl, benzoxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4 benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2 d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2 a]pyridinyl, carbazolyl, cinnolynyl, cyclopenta[d]pyrimidinyl, 6,7 dihydro 5H cyclopenta[4,5]thieno[2,3 d]pyrimidinyl, 5,6 dihydrobenzo[h]quinazolinyl, 5,6 dihydrobenzo[h]cinnolynyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2 c]pyridinyl, 5,6,7,8,9,10 hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10 hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10

hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, 5,8 methano 5,6,7,8 tetrahydroquinazoliny, naphthyridinyl, 1,6 naphthyridinonyl, oxadiazolyl, 2 oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a octahydrobenzo[h]quinazoliny, 1 phenyl 1H pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4 d]pyrimidinyl, pyridinyl, pyrido[3,2 d]pyrimidinyl, pyrido[3,4 d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazoliny, quinoxaliny, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8 tetrahydroquinazoliny, 5,6,7,8 tetrahydrobenzo[4,5]thieno[2,3 d]pyrimidinyl, 6,7,8,9 tetrahydro 5H cyclohepta[4,5]thieno[2,3 d]pyrimidinyl, 5,6,7,8 tetrahydropyrido[4,5 c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3 d]pyrimidinyl, thieno[3,2 d]pyrimidinyl, thieno[2,3 c]pyridinyl, and thiophenyl (i.e. thienyl).

[00188] The term "heterocycloalkyl" refers to a saturated ring with carbon atoms and at least one heteroatom. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycloalkyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. The heteroatoms in the heterocycloalkyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl is attached to the rest of the molecule through any atom of the heterocycloalkyl, valence permitting, such as any carbon or nitrogen atoms of the heterocycloalkyl. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholiny, octahydroindolyl, octahydroisoindolyl, 2 oxopiperazinyl, 2 oxopiperidinyl, 2 oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4 piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholiny, thiamorpholiny, 1 oxo thiomorpholiny, 2-oxa-6-azaspiro[3.3]heptane, and 1,1 dioxo thiomorpholiny.

[00189] The term "heterocycloalkenyl" refers to an unsaturated ring with carbon atoms and at least one heteroatom and there is at least one double bond between two ring carbons. Heterocycloalkenyl does not include heteroaryl rings. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycloalkenyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 5- to 12-membered bridged rings. In other embodiments, a heterocycloalkenyl comprises five to seven ring atoms. The heterocycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls include, e.g., pyrroline (dihydropyrrole), pyrazoline (dihydropyrazole), imidazoline (dihydroimidazole), triazoline (dihydrotriazole), dihydrofuran, dihydrothiophene, oxazoline (dihydrooxazole), isoxazoline (dihydroisoxazole), thiazoline (dihydrothiazole), isothiazoline (dihydroisothiazole), oxadiazoline (dihydrooxadiazole), thiadiazoline (dihydrothiadiazole), dihydropyridine, tetrahydropyridine, dihydropyridazine, tetrahydropyridazine, dihydropyrimidine, tetrahydropyrimidine, dihydropyrazine, tetrahydropyrazine, pyran, dihydropyran, thiopyran, dihydrothiopyran, dioxine, dihydrodioxine, oxazine, dihydrooxazine, thiazine, and dihydrothiazine.

[00190] The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., an NH or NH₂ of a compound. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, i.e., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds.

[00191] In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro (-NO₂), imino (=N-H), oximo (=N-OH), hydrazino (=N-NH₂), -Rb ORa, -Rb OC(O) Ra, -Rb OC(O) ORa, -Rb OC(O) N(Ra)₂, -Rb N(Ra)₂, -Rb C(O)Ra, -Rb C(O)ORa, -Rb C(O)N(Ra)₂, -Rb O Rc C(O)N(Ra)₂, -Rb N(Ra)C(O)ORa, -Rb N(Ra)C(O)Ra, -Rb N(Ra)S(O)tRa (where t is 1 or 2), -Rb S(O)tRa (where t is 1 or 2), -Rb S(O)tORa (where t is 1 or 2), and -Rb S(O)tN(Ra)₂ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro (-NO₂), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH₂), -Rb ORa, -Rb OC(O) Ra, -Rb OC(O) ORa, -Rb OC(O) N(Ra)₂, -Rb N(Ra)₂, -Rb C(O)Ra, -Rb C(O)ORa, -Rb C(O)N(Ra)₂, -Rb O Rc C(O)N(Ra)₂, -Rb N(Ra)C(O)ORa, -Rb N(Ra)C(O)Ra, -Rb N(Ra)S(O)tRa (where t is 1 or 2), -Rb S(O)tRa (where t is 1 or 2), -Rb S(O)tORa (where t is 1 or 2) and -Rb S(O)tN(Ra)₂ (where t is 1 or 2); wherein each Ra is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each Ra, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro (-NO₂), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH₂), -Rb ORa, -Rb OC(O) Ra, -Rb OC(O) ORa, -Rb OC(O) N(Ra)₂, -Rb N(Ra)₂, -Rb C(O)Ra, -Rb C(O)ORa, -Rb C(O)N(Ra)₂, -Rb O Rc C(O)N(Ra)₂, -Rb N(Ra)C(O)ORa, -Rb N(Ra)C(O)Ra, -Rb N(Ra)S(O)tRa (where t is 1 or 2), -Rb S(O)tRa (where t is 1 or 2), -Rb S(O)tORa (where t is 1 or 2) and -Rb S(O)tN(Ra)₂ (where t is 1 or 2); and wherein each Rb is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each Rc is a straight or branched alkylene, alkenylene or alkynylene chain.

[00192] Double bonds to oxygen atoms, such as oxo groups, are represented herein as both “=O” and “(O)”. Double bonds to nitrogen atoms are represented as both “=NR” and “(NR)”. Double bonds to sulfur atoms are represented as both “=S” and “(S)”.

[00193] In some embodiments, a "derivative" polypeptide or peptide is one that is modified, for example, by glycosylation, pegylation, phosphorylation, sulfation, reduction/alkylation, acylation, chemical coupling, or mild formalin treatment. A derivative may also be modified to contain a detectable label, either directly or indirectly, including, but not limited to, a radioisotope, fluorescent, and enzyme label.

[00194] Some embodiments refer to nucleic acid sequence information. It is contemplated that in some embodiments, thymine (T) may be interchanged with uracil (U), or vice versa. For example, some sequences in the sequence listing may recite Ts, but these may be replaced with Us in some embodiments. In some oligonucleotides with nucleic acid sequences that include uracil, the uracil may be replaced with thymine. Similarly, in some oligonucleotides with nucleic acid sequences that include thymine, the thymine may be replaced with uracil. In some embodiments, an oligonucleotide such as an siRNA comprises or consists of RNA. In some embodiments, the oligonucleotide may comprise or consist of DNA. For example, an ASO may include DNA.

[00195] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

VI. EXAMPLES

Example 1: Variants in genes encoding the receptor *MST1R* and its ligand *MST1* demonstrate protective associations for obstructive lung diseases and related traits

[00196] Variants in *MST1R* and *MST1* were evaluated for associations with lung diseases and related pulmonary and leukocyte traits in approximately 382,000 individuals with genotype data from the UK Biobank cohort. Variants evaluated included: (1) rs3020779, a common (AAF=0.82) *MST1* synonymous variant (Pro153Pro; P153P) which is a *MST1R* lung ↓ eQTL (2) rs142690032, a low-frequency (AAF=0.02) *MST1* stop-gained variant (Arg651Ter; R651Ter) which prematurely terminates MSP at amino acid 651, and (3) rs3197999, a common (AAF=0.29) *MST1* missense variant (Arg703Cys; R703C) which has been experimentally characterized as impairing MSP's ability to bind *MST1R*. The rs3020779 variant was considered a hypomorphic *MST1R* variant that may result in a decrease in the abundance and/or activity of the *MST1R* gene product. The rs142690032 and rs3197999 variants were also considered to result in a decrease in abundance or activity of the *MST1* gene product, and thus result in a decrease in signaling through the *MST1R* gene product.

[00197] Analyses used a logistic or linear regression model with age, sex and the first ten principal components of genetic ancestry as covariates. The analyses resulted in identification of associations for the individual *MST1R* and *MST1* variants (**Table 1A, 1B, 2A, and 2B**). For example, there were protective associations with multiple lung-disease-related traits. The evaluated variants were associated with protection from COPD, asthma and lower risk of inhaled beta agonist prescription (**Table 1A and 1B**). Additionally, the evaluated variants were associated with increased lung function (FEV1 and FVC) and decreased circulating neutrophil counts (**Table 2A and Table 2B**).

Table 1A. *MST1R* and *MST1* lung disease associations

Variant	Gene	Function	AAF	COPD (n=22,308)	
				P value	OR
rs3020779	<i>MST1R</i>	MST1R eQTL	0.82	4.33E-09	↓0.941
rs142690032	<i>MST1</i>	Stop-Gained; R651Ter	0.02	4.07E-07	↓0.859
rs3197999	<i>MST1</i>	Missense; R703C; MST1 pQTL	0.29	2.16E-05	↓0.962

Table 1B. *MST1R* and *MST1* lung disease associations

Variant	Asthma (n=58,257)		Family History of COPD (n=60,301)		Inhaled Beta Agonist Medication (n=31,028)	
	P value	OR	P value	OR	P value	OR
rs3020779	4.57E-04	↓0.979	0.004	↓0.985	5.32E-05	↓0.969
rs142690032	0.004	↓0.955	0.105	↓0.980	4.47E-04	↓0.931
rs3197999	0.002	↓0.983	0.001	↓0.984	2.56E-06	↓0.968

Table 2A. *MST1R* and *MST1* lung function and neutrophil associations

Variant	Gene	Function	AAF	FEV1 (n=287,050)	
				P value	Beta
rs3020779	<i>MST1R</i>	MST1R eQTL	0.82	3.06E-10	↑0.002
rs142690032	<i>MST1</i>	Stop-Gained; R651Ter	0.02	0.003	↑0.015
rs3197999	<i>MST1</i>	Missense; R703C; MST1 pQTL	0.29	3.29E-15	↑0.002

Table 2B. *MST1R* and *MST1* lung function and neutrophil associations

Variant	FVC (n=286,925)		FEV1/FVC Ratio (n=286,523)		Neutrophil Count (n=366,089)	
	P value	Beta	P value	Beta	P value	Beta
rs3020779	2.41E-06	↑0.001	9.32E-09	↑0.019	0.01	↓-0.010
rs142690032	0.002	↑0.003	0.789	↑-0.003	0.005	↓-0.034
rs3197999	1.03E-11	↑0.002	0.004	↑0.008	8.2E-08	↓-0.018

[00198] These results indicate that reduced abundance or activity of *MST1R*, and decreased *MST1R* signaling via reduced MSP abundance or activity, may protect against COPD or asthma, improve lung function, or lower circulating neutrophils, which may be pro-inflammatory cells involved in obstructive airway disease. These results further indicate that therapeutic inhibition of *MST1R* may result in similar disease-protective effects.

Example 2: Bioinformatic selection of sequences in order to identify therapeutic siRNAs to downmodulate expression of the *MST1R* mRNA

[00199] Screening sets were defined based on bioinformatic analysis. Therapeutic siRNAs were designed to target human *MST1R*, and the *MST1R* sequence of at least one toxicology-relevant species, in this case, the non-human primates (NHP) rhesus and cynomolgus monkeys. Drivers for the design of the screening set were predicted specificity of the siRNAs against the transcriptome of the relevant species as well as cross-reactivity between species. Predicted specificity in human, rhesus monkey, cynomolgus monkey, mouse and rat was determined for sense (S) and antisense (AS) strands. These were assigned a

“specificity score” which considers the likelihood of unintended downregulation of any other transcript by full or partial complementarity of an siRNA strand (up to 4 mismatches within positions 2-18) as well as the number and positions of mismatches. Thus, off-target(s) for antisense and sense strands of each siRNA were identified. In addition, the number of potential off-targets was used as an additional specificity factor in the specificity score. As identified, siRNAs with high specificity and a low number of predicted off-targets provide a benefit of increased targeting specificity.

[00200] In addition to selecting siRNA sequences with high sequence specificity to *MST1R* mRNA, siRNA sequences within the seed region were analyzed for similarity to seed regions of known miRNAs. siRNAs can function in a miRNA like manner via base-pairing with complementary sequences within the 3'-UTR of mRNA molecules. The complementarity typically encompasses the 5'-bases at positions 2-7 of the miRNA (seed region). To circumvent siRNAs to act via functional miRNA binding sites, siRNA strands containing natural miRNA seed regions were avoided. Seed regions identified in miRNAs from human, mouse, rat, rhesus monkey, dog, rabbit and pig are referred to as “conserved”. Combining the “specificity score” with miRNA seed analysis yielded a “specificity category”. This is divided into categories 1-4, with 1 having the highest specificity and 4 having the lowest specificity. Each strand of the siRNA is assigned to a specificity category.

[00201] Specificity and species cross-reactivity was assessed for human, cynomolgus monkey, rhesus monkey, mouse and rat *MST1R*. The analysis was based on a canonical siRNA design using 19 bases and 17 bases (without considering positions 1 and 19) for cross-reactivity. Full match as well as single mismatch analyses were included.

[00202] Analysis of the human Single Nucleotide Polymorphism (SNP) database (NCBI-DB-SNP) to identify siRNAs targeting regions with known SNPs was also carried out to identify siRNAs that may be non-functional in individuals containing the SNP. Information regarding the positions of SNPs within the target sequence as well as minor allele frequency (MAF) in case data was obtained in this analysis.

[00203] Initial analysis of the relevant *MST1R* mRNA sequence revealed few sequences that fulfil the specificity parameters and at the same time target *MST1R* mRNA in all of the analyzed relevant species. Therefore, it was decided to design independent screening subsets for the therapeutic siRNAs.

[00204] The siRNAs in these subsets recognize the human, cynomolgus monkey, rhesus monkey *MST1R* sequences. Therefore, the siRNAs in these subsets can be used to target human *MST1R* in a therapeutic setting.

[00205] The number of siRNA sequences that can be derived from human *MST1R* mRNA (ENST00000296474.8, SEQ ID NO: 9818) without consideration of specificity or species cross-reactivity was 4754 (sense and antisense strand sequences included in SEQ ID NOS: 1-9508).

[00206] Prioritizing sequences for target specificity, species cross-reactivity, miRNA seed region sequences and SNPs as described above yields subset A. Subset A contains 336 siRNAs whose base sequences are shown in **Table 3**.

Table 3. Sequences in siRNA subset A

SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
469	GCUGUGUUUGUAGCCAUAC	5223	GUAUGGCUACAAACACAGC
471	UGUGUUUGUAGCCAUACGC	5225	GCGUAUGGCUACAAACACA
472	GUGUUUGUAGCCAUACGCA	5226	UGCGUAUGGCUACAAACAC
473	UGUUUGUAGCCAUACGCAA	5227	UUGCGUAUGGCUACAAACA
474	GUUUUGUAGCCAUACGCAU	5228	AUUGCGUAUGGCUACAAAC
475	UUUGUAGCCAUACGCAAUC	5229	GAUUGCGUAUGGCUACAAA
476	UUGUAGCCAUACGCAAUCG	5230	CGAUUGCGUAUGGCUACAA
477	UGUAGCCAUACGCAAUCGC	5231	GCGAUUGCGUAUGGCUACA
478	GUAGCCAUACGCAAUCGCC	5232	GGCGAUUGCGUAUGGCUAC
479	UAGCCAUACGCAAUCGCCU	5233	AGGCGAUUGCGUAUGGCUA
480	AGCCAUACGCAAUCGCCUG	5234	CAGGCGAUUGCGUAUGGCU
481	GCCAUACGCAAUCGCCUGC	5235	GCAGGCGAUUGCGUAUGGC
482	CCAUACGCAAUCGCCUGCA	5236	UGCAGGCGAUUGCGUAUGG
483	CAUACGCAAUCGCCUGCAU	5237	AUGCAGGCGAUUGCGUAUG
557	ACCCUGGCUGCCAGACGUG	5311	CACGUCUGGCAGCCAGGGU
562	GGCUGCCAGACGUGUGCAG	5316	CUGCACACGUCUGGCAGCC
564	CUGCCAGACGUGUGCAGCC	5318	GGCUGCACACGUCUGGCAG
568	CAGACGUGUGCAGCCUGUG	5322	CACAGGCGUCACACGUCUG
691	UGCUUCCUGCAUGACCUAG	5445	CUAGGUCAUGCAGGAAGCA
692	GCUUCCUGCAUGACCUAGA	5446	UCUAGGUCAUGCAGGAAGC
693	CUUCCUGCAUGACCUAGAG	5447	CUUAGGUCAUGCAGGAAG
717	AGGGACAGCCGUGCAUCUG	5471	CAGAUGCACGGCUGUCCCU
718	GGGACAGCCGUGCAUCUGG	5472	CCAGAUGCACGGCUGUCCC
721	ACAGCCGUGCAUCUGGCAG	5475	CUGCCAGAUGCACGGCUGU
722	CAGCCGUGCAUCUGGCAGC	5476	GCUGCCAGAUGCACGGCUG
723	AGCCGUGCAUCUGGCAGCG	5477	CGCUGCCAGAUGCACGGCU
724	GCCGUGCAUCUGGCAGCGC	5478	GCGCUGCCAGAUGCACGGC
725	CCGUGCAUCUGGCAGCGCC	5479	GGCGCUGCCAGAUGCACGG
726	CGUGCAUCUGGCAGCGCCA	5480	UGGCGCUGCCAGAUGCACG
753	CUUCUCAGCCACCAUAAC	5507	GUUAUGGUGGGCUGAGAAG
759	AGCCACCAUAACCGGCC	5513	GGGCCGGUUAUGGUGGGCU
761	CCCACCAUAACCGGCCCGA	5515	UCGGGCCGGUUAUGGUGGG
762	CCACCAUAACCGGCCCGAU	5516	AUCGGGCCGGUUAUGGUGG
763	CACCAUAACCGGCCCGAUG	5517	CAUCGGGCCGGUUAUGGUG
764	ACCAUAACCGGCCCGAUGA	5518	UCAUCGGGCCGGUUAUGGU
765	CCAUAACCGGCCCGAUGAC	5519	GUCAUCGGGCCGGUUAUGG
766	CAUAACCGGCCCGAUGACU	5520	AGUCAUCGGGCCGGUUAUG
767	AUAACCGGCCCGAUGACUG	5521	CAGUCAUCGGGCCGGUUAU
775	CCCGAUGACUGCCCGACU	5529	AGUCGGGGCAGUCAUCGGG
776	CCGAUGACUGCCCGACUG	5530	CAGUCGGGGCAGUCAUCGG
777	CGAUGACUGCCCGACUGU	5531	ACAGUCGGGGCAGUCAUCG
801	CAGCCCAUUGGGCACCUGU	5555	ACGGGUGCCCAAUGGGCUG
804	CCCAUUGGGCACCCGUGUA	5558	UACACGGGUGCCCAAUGGG
824	CUGUGGUUGAGCAAGGCCA	5578	UGGCCUUGCUCAACCACAG
826	GUGGUUGAGCAAGGCCAGG	5580	CCUGGCCUUGCUCAACCAC
837	AGGCCAGGCCUCCUAUUUC	5591	GAAAUAGGAGGCCUGGCCU
842	AGGCCUCCUAUUUCUACGU	5596	ACGUAGAAUAGGAGGCCU
845	CCUCCUAUUUCUACGUGGC	5599	GCCACGUAGAAUAGGAGG
854	UCUACGUGGCAUCCUCACU	5608	AGUGAGGAUCCACGUAGA
855	CUACGUGGCAUCCUCACUG	5609	CAGUGAGGAUCCACGUAG
863	CAUCCUCACUGGACGCAGC	5617	GCUGCGUCCAGUGAGGAUG
864	AUCCUCACUGGACGCAGCC	5618	GGCUGCGUCCAGUGAGGAU
866	CCUCACUGGACGCAGCCGU	5620	ACGGCUGCGUCCAGUGAGG
888	UGCCAGCUUCAGCCACGC	5642	GCGUGGGCUGAAGCUGGCA
895	UUCAGCCCACGCUCAGUGU	5649	ACACUGAGCGUGGGCUGAA
897	CAGCCCACGCUCAGUGUCU	5651	AGACACUGAGCGUGGGCUG
898	AGCCCACGCUCAGUGUCUA	5652	UAGACACUGAGCGUGGGCU
899	GCCCACGCUCAGUGUCUAU	5653	AUAGACACUGAGCGUGGGC

900	CCCACGCUCAGUGUCUAUC	5654	GAUAGACACUGAGCGUGGG
901	CCACGCUCAGUGUCUAUCA	5655	UGAUAGACACUGAGCGUGG
903	ACGCUCAGUGUCUAUCAGG	5657	CCUGAUAGACACUGAGCGU
904	CGCUCAGUGUCUAUCAGGC	5658	GCCUGAUAGACACUGAGCG
907	UCAGUGUCUAUCAGGCUGC	5661	GACGCCUGAUAGACACUGA
908	CAGUGUCUAUCAGGCUGCUC	5662	AGACGCCUGAUAGACACUG
909	AGUGUCUAUCAGGCUGCUC	5663	GAGACGCCUGAUAGACACU
910	GUGUCUAUCAGGCUGCUC	5664	UGAGACGCCUGAUAGACAC
911	UGUCUAUCAGGCUGCUC	5665	UUAGACGCCUGAUAGACA
912	GUCUAUCAGGCUGCUC	5666	CUUGAGACGCCUGAUAGAC
913	UCUAUCAGGCUGCUC	5667	CCUUGAGACGCCUGAUAGA
915	UAUCAGGCUGCUC	5669	AGCCUUGAGACGCCUGAUA
948	CGCACCGGGCUUUGUGGCG	5702	CGCCACAAAGCCCGUGGCG
966	GUUGUCAGUGCUGCCCAAG	5720	CUUGGGCAGCACUGACAAC
976	CUGCCCAAGCAUCUUGUCUC	5730	AGACAAGAUGCUGGGCAG
977	UGCCCAAGCAUCUUGUCUC	5731	GAGACAAGAUUCUUGGGCA
985	CAUCUUGUCUCCUACAGUA	5739	UACUGUAGGAGACAAGAUG
986	AUCUUGUCUCCUACAGUAU	5740	AUACUGUAGGAGACAAGAU
989	UUGUCUCCUACAGUAUUGA	5743	UCAAUACUGUAGGAGACAA
990	UGUCUCCUACAGUAUUGAA	5744	UUCAAUACUGUAGGAGACA
992	UCUCCUACAGUAUUGAAUA	5746	UAUUCAAUACUGUAGGAGA
1001	GUAUUGAAUACGUGCACAG	5755	CUGUGCACGUAUUCAAUAC
1003	AUUGAAUACGUGCACAGCU	5757	AGCUGUGCACGUAUUCAAU
1004	UUGAAUACGUGCACAGCUU	5758	AAGCUGUGCACGUAUUCAA
1005	UGAAUACGUGCACAGCUUC	5759	GAAGCUGUGCACGUAUUC
1006	GAAUACGUGCACAGCUUCC	5760	GGAAGCUGUGCACGUAUUC
1042	UACUUCUGACUGUACAGC	5796	GCUGUACAGUCAGGAAGUA
1043	ACUUCUGACUGUACAGCC	5797	GGCUGUACAGUCAGGAAGU
1046	UCCUGACUGUACAGCCGGC	5800	GCCGGCUGUACAGUCAGGA
1048	CUGACUGUACAGCCGGCCA	5802	UGGCCGGCUGUACAGUCAG
1049	UGACUGUACAGCCGGCCAG	5803	CUGGCCGGCUGUACAGUCA
1050	GACUGUACAGCCGGCCAGC	5804	GCUGGCCGGCUGUACAGUC
1051	ACUGUACAGCCGGCCAGCG	5805	CGCUGGCCGGCUGUACAGU
1053	UGUACAGCCGGCCAGCGUG	5807	CACGUGGCCGGCUGUACA
1054	GUACAGCCGGCCAGCGUGA	5808	UCACGUGGCCGGCUGUAC
1055	UACAGCCGGCCAGCGUGAC	5809	GUACGUGGCCGGCUGUA
1111	CUUAGCGCCACUGAGCCAG	5865	CUGGCUAGUGGCGCUAAG
1121	CUGAGCCAGAGUUGGGUGA	5875	UCACCCAAUCUGGCUAG
1124	AGCCAGAGUUGGGUGACUA	5878	UAGUACCCAAUCUGGCU
1129	GAGUUGGGUGACUAUCGGG	5883	CCCGAUAGUACCCAAUC
1130	AGUUGGGUGACUAUCGGGA	5884	UCCCGAUAGUACCCAAUC
1131	GUUGGGUGACUAUCGGGAG	5885	CUCCCGAUAGUACCCAA
1132	UUGGGUGACUAUCGGGAGC	5886	GCUCCGAUAGUACCCAA
1134	GGGUGACUAUCGGGAGCUG	5888	CAGCUCCGAUAGUACCC
1137	UGACUAUCGGGAGCUGGUC	5891	GACCAGCUCCGAUAGUCA
1138	GACUAUCGGGAGCUGGUCC	5892	GGACCAGCUCCGAUAGUC
1139	ACUAUCGGGAGCUGGUCCU	5893	AGGACCAGCUCCGAUAGU
1145	GGGAGCUGGUCCUCGACUG	5899	CAGUCGAGGACCAGCUC
1146	GGAGCUGGUCCUCGACUGC	5900	GCAGUCGAGGACCAGCUC
1147	GAGCUGGUCCUCGACUGCA	5901	UGCAGUCGAGGACCAGCUC
1152	GUCCUCGACUGCAGAUUU	5906	AAAUUCGACUGGAGGACC
1153	GUCCUCGACUGCAGAUUUG	5907	CAAAUCGACUGGAGGAC
1154	UCCUCGACUGCAGAUUUGC	5908	GCAAAUCGACUGGAGGA
1155	CCUCGACUGCAGAUUUGCU	5909	AGCAAAUCGACUGGAGG
1156	CUCGACUGCAGAUUUGCUC	5910	GAGCAAAUCGACUGGAG
1157	UCGACUGCAGAUUUGCUCC	5911	GGAGCAAAUCGACUGGAG
1158	CGACUGCAGAUUUGCUCCA	5912	UGGAGCAAAUCGACUGG
1161	CUGCAGAUUUGCUCCAAA	5915	UUUUGGAGCAAAUCGAG
1162	UGCAGAUUUGCUCCAAAC	5916	GUUUUGGAGCAAAUCGAG
1164	CAGAUUUGCUCCAAACGC	5918	GCGUUUGGAGCAAAUCG
1165	AGAUUUGCUCCAAACGCA	5919	UGCGUUUGGAGCAAAUCU

1166	GAUUUGCUCCAAAACGCAG	5920	CUGCGUUUUGGAGCAAAUC
1170	UGCUCCAAAAACGCAGGCGC	5924	GCGCCUGCGUUUUGGAGCA
1171	GCUCCAAAAACGCAGGCGCC	5925	GGCGCCUGCGUUUUGGAGC
1172	CUCCAAAACGCAGGCGCCG	5926	CGGCGCCUGCGUUUUGGAG
1173	UCCAAAACGCAGGCGCCG	5927	CCGGCGCCUGCGUUUUGGA
1204	GGCGGACAGCCCUACCCUG	5958	CAGGGUAGGGCUGUCCGCC
1350	CAACUCUGUCGUCGUGGCC	6104	GGCACAAGACGACAGAGUUG
1356	UGUCGUCUGUGCCUUCGCC	6110	GGGGAAGGCACAGACGACA
1405	GGUGUGGAGCGCUGUUGUG	6159	CACAACAGCGCUCCACACC
1406	GUGUGGAGCGCUGUUGUGA	6160	UCACAACAGCGCUCCACAC
1408	GUGGAGCGCUGUUGUGAAU	6162	AUUCACAACAGCGCUCCAC
1409	UGGAGCGCUGUUGUGAAUC	6163	GAUUCACAACAGCGCUCCA
1411	GAGCGCUGUUGUGAAUCCC	6165	GGGAUUCACAACAGCGCUC
1421	GUGAAUCCCCAGUCCAUC	6175	GGAUUGACUGGGGAUUCAC
1443	CCUCCGGCGAGGCCUCGAC	6197	GUUCGAGGCCUCGCCGGAGG
1444	CUCCGGCGAGGCCUCGACU	6198	AGUCGAGGCCUCGCCGGAG
1445	UCCGGCGAGGCCUCGACUU	6199	AAGUCGAGGCCUCGCCGGA
1446	CCGGCGAGGCCUCGACUUC	6200	GAAGUCGAGGCCUCGCCGG
1447	CGGCGAGGCCUCGACUUCU	6201	AGAAGUCGAGGCCUCGCCG
1476	CAGUUUUUGCCCAACCCG	6230	CGGGUUGGGGCAAAAACUG
1857	GACCUGUGGGCGUUGCCUA	6611	UAGGCAACGCCACAGGUC
1858	ACCUUGUGGGCGUUGCCUAA	6612	UUAGGCAACGCCACAGGU
1862	GUGGGCGUUGCCUAAGGGC	6616	GCCCUUAGGCAACGCCCAC
1863	UGGGCGUUGCCUAAGGGCA	6617	UGCCCUUAGGCAACGCCCA
1969	CCUAAGCUUACUGAGUUC	6723	GGAAUCAGUAAGCUUAGG
2124	CAAGGACAGCUCAAAACUC	6878	GAGUUUUGAGCUGUCCUUG
2125	AAGGACAGCUCAAAACUCA	6879	UGAGUUUUGAGCUGUCCUU
2142	CAGACCAGUGCCCCGGAAA	6896	UUUCGGGGCACUGGUCUG
2143	AGACCAGUGCCCCGGAAAG	6897	CUUUCCGGGGCACUGGUCU
2144	GACCAGUGCCCCGGAAAGA	6898	UCUUUCGGGGCACUGGUC
2148	AGUGCCCCGGAAAGACUUU	6902	AAAGUCUUUCGGGGCACU
2149	GUGCCCCGGAAAGACUUUG	6903	CAAAGUCUUUCGGGGCAC
2150	UGCCCCGGAAAGACUUUGU	6904	ACAAAGUCUUUCGGGGCA
2151	GCCCCGGAAAGACUUUGUA	6905	UACAAAGUCUUUCGGGGC
2152	CCCCGGAAAGACUUUGUAG	6906	CUACAAAGUCUUUCGGGG
2153	CCCGAAAGACUUUGUAGA	6907	UCUACAAAGUCUUUCGGG
2154	CCGGAAAGACUUUGUAGAG	6908	CUUACAAAGUCUUUCGG
2165	UUGUAGAGGAGUUUGAGUG	6919	CACUCAAAUCUCCUCAAA
2180	AGUGUGAACUGGAGCCCUU	6934	AAGGGCUCAGUUCACACU
2208	GGCAGUGGGGCCUACCAAC	6962	GUUGGUAGGCCCCACUGCC
2226	CGUCAGCCUCACCGUGACU	6980	AGUCACGGUGAGGCUGACG
2228	UCAGCCUCACCGUGACUAA	6982	UUAGUCACGGUGAGGCUGA
2229	CAGCCUCACCGUGACUAAC	6983	GUUAGUCACGGUGAGGCUG
2230	AGCCUCACCGUGACUAACA	6984	UGUUAGUCACGGUGAGGCU
2232	CCUCACCGUGACUAACAUG	6986	CAUGUUAGUCACGGUGAGG
2233	CUCACCGUGACUAACAUGC	6987	GCAUGUAGUCACGGUGAG
2234	UCACCGUGACUAACAUGCC	6988	GGCAUGUUAGUCACGGUGA
2235	CACCGUGACUAACAUGCCA	6989	UGGCAUGUAGUCACGGUG
2237	CCGUGACUAACAUGCCACC	6991	GGUGGCAUGUAGUCACGG
2240	UGACUAACAUGCCACCGGG	6994	CCCGGUGGCAUGUAGUCA
2241	GACUAACAUGCCACCGGGC	6995	GCCCCGUGGCAUGUAGUC
2242	ACUAACAUGCCACCGGGCA	6996	UGCCCGGUGGCAUGUAGU
2243	CUAACAUGCCACCGGGCAA	6997	UUGCCCGGUGGCAUGUAG
2244	UAACAUGCCACCGGGCAAG	6998	CUUGCCCGGUGGCAUGUUA
2245	AACAUGCCACCGGGCAAGC	6999	GCUUGCCCGGUGGCAUGUU
2246	ACAUGCCACCGGGCAAGCA	7000	UGCUUGCCCGGUGGCAUGU
2252	CACCGGGCAAGCACUUCGG	7006	CGGAAGUGCUUGCCCGGUG
2253	ACCGGGCAAGCACUUCGG	7007	CCGGAAGUGCUUGCCCGGU
2257	GGCAAGCACUUCGGGUAG	7011	CUACCCGGAAGUGCUUGCC
2258	GCAAGCACUUCGGGUAGA	7012	UCUACCCGGAAGUGCUUGC
2259	CAAGCACUUCGGGUAGAC	7013	GUCUACCCGGAAGUGCUUG

2263	CACUCCGGGUAGACGGCA	7017	UGCCGUCUACCCGGAAGUG
2264	ACUUCGGGUAGACGGCAC	7018	GUGCCGUCUACCCGGAAGU
2265	CUUCGGGUAGACGGCAC	7019	GGUGCCGUCUACCCGGAAG
2266	UUCGGGUAGACGGCACCU	7020	AGGUGCCGUCUACCCGGA
2267	UCCGGGUAGACGGCACCU	7021	GAGGUGCCGUCUACCCGGA
2269	CGGGUAGACGGCACCUCCG	7023	CGGAGGUGCCGUCUACCCG
2318	UGCUGAUGCAGUGCAACC	7072	GGUUGCACUGCUAUCAGCA
2319	GCUGAUGCAGUGCAACCC	7073	GGGUUGCACUGCUAUCAGC
2320	CUGAUGCAGUGCAACCCC	7074	GGGUUGCACUGCUAUCAG
2322	GAUAGCAGUGCAACCCUC	7076	GAGGGUUGCACUGCUAUC
2332	CAACCCUCUUGGCCAC	7086	GUGGGCAAAGAGGGGUUG
2366	GUCUCACUCUUGAAGGCCA	7120	UGGCCUUAAGAGUGAGAC
2369	UCACUCUUGAAGGCCAGAG	7123	CUCUGGCCUUAAGAGUGA
2371	ACUCUUGAAGGCCAGAGUC	7125	GACUCUGGCCUUAAGAGU
2386	AGUCUGUCUGUAGGCCCA	7140	UGGUGCCUACAGACAGACU
2412	UGUGCUGGUCUUGGGACU	7166	AGUCCAUUGACCAGCACA
2413	GUGCUGGUCUUGGGACUG	7167	CAGUCCAUUGACCAGCAC
2418	GGUCAUUGGGACUGAGUGU	7172	ACACUCAGUCCAUUGACC
2420	UCAAUGGGACUGAGUGUCU	7174	AGACACUCAGUCCAUUGA
2421	CAAUGGGACUGAGUGUCUG	7175	CAGACACUCAGUCCAUUG
2422	AAUGGGACUGAGUGUCUGC	7176	GCAGACACUCAGUCCAUU
2425	GGGACUGAGUGUCGUAG	7179	CUAGCAGACACUCAGUCCC
2427	GACUGAGUGUCGUAGCA	7181	UGCUAGCAGACACUCAGUC
2430	UGAGUGUCUGCUAGCACGG	7184	CCGUGCUAGCAGACACUCA
2432	AGUGUCUGCUAGCACGGGU	7186	ACCCGUGCUAGCAGACACU
2435	GUCUGCUAGCACGGGUCAG	7189	CUGACCCGUGCUAGCAGAC
2437	CUGCUAGCACGGGUCAGUG	7191	CACUGACCCGUGCUAGCAG
2438	UGCUGACACGGGUCAGUGA	7192	UCACUGACCCGUGCUAGCA
2440	CUAGCACGGGUCAGUGAGG	7194	CCUCACUGACCCGUGCUAG
2443	GCACGGGUCAGUGAGGGGC	7197	GCCCCUCACUGACCCGUGC
2445	ACGGGUCAGUGAGGGGCAG	7199	CUGCCCCUCACUGACCCGU
2455	GAGGGGCAGCUUUAUGUG	7209	CACAUAAAAGCUGCCCCUC
2460	GCAGCUUUAUGUGCCACA	7214	UGUGGCACAUAAAAGCUGC
2462	AGCUUUAUGUGCCACACC	7216	GGUGUGGCACAUAAAAGCU
2464	CUUUAUGUGCCACACCCC	7218	GGGGUGUGGCACAUAAAAG
2566	GAAGACCCUGUCGUUAA	7320	UUAGCACGACAGGGUCUUC
2567	AAGACCCUGUCGUUAAAG	7321	CUUAGCACGACAGGGUCUU
2571	CCUGUCGUGCUAAGCAUC	7325	GAUGCUUAGCACGACAGGG
2572	CCUGUCGUGCUAAGCAUCA	7326	UGAUGCUUAGCACGACAGG
2575	GUCGUGCUAAGCAUCAGCC	7329	GGCUGAUGCUUAGCACGAC
2577	CGUGCUAAGCAUCAGCCCC	7331	GGGGCUGAUGCUUAGCACG
2581	CUAAGCAUCAGCCCCAACU	7335	AGUUGGGCUGAUGCUUAG
2582	UAAGCAUCAGCCCCAACUG	7336	CAGUUGGGCUGAUGCUUA
2584	AGCAUCAGCCCCAACUGUG	7338	CACAGUUGGGCUGAUGCU
2628	CUGUGGCCAGCAUCUAACU	7382	AGUUAGAUGCUGGCCACAG
2629	UGUGGCCAGCAUCUAACUU	7383	AAGUUAAGUUGCUGGCCACA
2644	ACUUCAGCAUGGCACUUAAG	7398	CUAAGUGCCAUGCUGAAGU
2646	UUCAGCAUGGCACUUAAGUG	7400	CACUAGUGCCAUGCUGAAG
2648	CAGCAUGGCACUUAAGUCU	7402	AGCACUAGUGCCAUGCUG
2652	AUGGCACUUAAGUCUGUCA	7406	UGACAGCACUAGUGCCAUC
2655	GCACUUAAGUCUGUCAUUC	7409	GAAUGACAGCACUAGUGC
2656	CACUUAAGUCUGUCAUUC	7410	GGAAUGACAGCACUAGUG
2661	AGUGCUGUCAUCCAUAGAC	7415	GUCAUGGAAUGACAGCACU
2663	UGCUGUCAUCCAUAGACGG	7417	CCGUCUUGGAAUGACAGCA
2664	GCUGUCAUCCAUAGACGGG	7418	CCCGUCAUGGAAUGACAGC
2666	UGUCAUCCAUAGACGGGCU	7420	AGCCCGUCAUGGAAUGACA
2668	UCAUCCAUAGACGGGCUUA	7422	UAAGCCCGUCAUGGAAUGA
2669	CAUCCAUAGACGGGCUUAG	7423	CUAAGCCCGUCAUGGAAUG
2670	AUCCAUAGACGGGCUUAGG	7424	CCUAAGCCCGUCAUGGAAU
2671	UCCAUAGACGGGCUUAGGG	7425	CCCUAAGCCCGUCAUGGAA
2673	CCAUGACGGGCUUAGGGCA	7427	UGCCCUAAGCCCGUCAUGG

2676	UGACGGGCUUAGGGCAGUG	7430	CACUGCCCUAAGCCCGUCA
2678	ACGGGCUUAGGGCAGUGGA	7432	UCCACUGCCCUAAGCCCGU
2808	AGCUGCUGGCUUACACUG	7562	CAGUGUAAAGCCAGCAGCU
2816	GCUUUAACUGCCUGGCUU	7570	AAGCCAGGCAGUGUAAAGC
2887	CCUGAGGAGCAUGCCAUUA	7641	UAAUGGCAUGCUCUCAGG
2889	UGAGGAGCAUGCCAUUAAG	7643	CUUAAUGGCAUGCUCUCA
2891	AGGAGCAUGCCAUUAAGUU	7645	AACUUAUUGGCAUGCUCU
2895	GCAUGCCAUUAAGUUUGAG	7649	CUCAAACUUAUUGGCAUGC
3084	UAUCCUGGGUAGAGUGGUG	7838	CACCACUCUACCCAGGAUA
3186	UGCACUGGUCUUCAGCUAC	7940	GUAGCUGAAGACCAGUGCA
3191	UGGUCUUCAGCUACUGGUG	7945	CACCAGUAGCUGAAGACCA
3192	GGUCUUCAGCUACUGGUGG	7946	CCACCAGUAGCUGAAGACC
3223	CUAGUUCUCCUCCCAACC	7977	GGUUGGGAGGAAGAACUAG
3279	CACACCCUGCCUAUUCUG	8033	CAGAAUAGGCAGGGGUGUG
3297	GUACUCGGGCUUGACUAC	8051	GUAGUCAGAGCCCGAGUAC
3298	UACUCGGGCUUGACUACA	8052	UGUAGUCAGAGCCCGAGUA
3299	ACUCGGGCUUGACUACAG	8053	CUGUAGUCAGAGCCCGAGU
3300	CUCGGGCUUGACUACAGA	8054	UCUGUAGUCAGAGCCCGAG
3301	UCGGGCUUGACUACAGAA	8055	UUCUGUAGUCAGAGCCCGA
3537	CCACUUUGGAGUUGUCUAC	8291	GUAGACAAUCCAAAGUGG
3538	CACUUUGGAGUUGUCUACC	8292	GGUAGACAACUCCAAAGUG
3560	GAGAAUACAUAGACCAGGC	8314	GCCUGGUCUAGUUAUUCUC
3563	AAUACAUAGACCAGGCCCA	8317	UGGGCCUGGUCUAGUUAU
3564	AUACAUAGACCAGGCCCAG	8318	CUGGGCCUGGUCUAGUUAU
3568	AUAGACCAGGCCCAGAAUC	8322	GAUUCUGGGCCUGGUCUUA
3570	AGACCAGGCCCAGAAUCGA	8324	UCGAUUCUGGGCCUGGUCU
3574	CAGGCCCAGAAUCGAAUCC	8328	GGAUUCGAUUCUGGGCCUG
3576	GGCCCAAGAAUCGAAUCCAA	8330	UUGGAUUCGAUUCUGGGCC
3577	GCCCAGAAUCGAAUCCAAU	8331	AUUGGAUUCGAUUCUGGGC
3578	CCCAGAAUCGAAUCCAAUG	8332	CAUUGGAUUCGAUUCUGGG
3580	CAGAAUCGAAUCCAAUGUG	8334	CACAUUGGAUUCGAUUCUG
3581	AGAAUCGAAUCCAAUGUGC	8335	GCACAUUGGAUUCGAUUCU
3582	GAAUCGAAUCCAAUGUGCC	8336	GGACAUUGGAUUCGAUUC
3583	AAUCGAAUCCAAUGUGCCA	8337	UGGCACAUUGGAUUCGAUU
3584	AUCGAAUCCAAUGUGCCA	8338	AUGGCACAUUGGAUUCGAU
3586	CGAAUCCAAUGUGCCAUCA	8340	UGAUGGCACAUUGGAUUCG
3587	GAAUCCAAUGUGCCAUCAA	8341	UUGAUGGCACAUUGGAUUC
3588	AAUCCAAUGUGCCAUCAAG	8342	CUUGAUGGCACAUUGGAUU
3592	CAAUGUGCCAUCAAGUCAC	8346	GUGACUUGAUGGCACAUUG
3594	AUGUGCCAUCAAGUCACUA	8348	UAGUGACUUGAUGGCACA
3595	UGUGCCAUCAAGUCACUAA	8349	UUAGUGACUUGAUGGCACA
3596	GUGCCAUCAAGUCACUAAG	8350	CUUAGUGACUUGAUGGCAC
3597	UGCCAUCAAGUCACUAAGU	8351	ACUUGAGUGACUUGAUGGCA
3600	CAUCAAGUCACUAAGUCGC	8354	GCGACUUGAGACUUGAUG
3655	GAGGGGCUUGCUCUAGCGUG	8409	CACGCAUGAGCAGCCCCUC
3656	AGGGGCUUGCUCUAGCGUGG	8410	CCACGCAUGAGCAGCCCCU
3657	GGGGCUUGCUCUAGCGUGGC	8411	GCCACGCAUGAGCAGCCCC
3659	GGCUGCUCUAGCGUGGCCU	8413	AGGCCACGCAUGAGCAGCC
3663	GCUCUAGCGUGGCCUGAAC	8417	GUUCAGGCCACGCAUGAGC
3666	CAUGCGUGGCCUGAACCCAC	8420	GUGGUUCAGGCCACGCAUG
3670	CGUGGCCUGAACCCACCCGA	8424	UCGGGUUGGUUCAGGCCACG
3671	GUGGCCUGAACCCACCCGAA	8425	UUCGGGUUGGUUCAGGCCAC
3672	UGGCCUGAACCCACCCGAAU	8426	AUUCGGGUUGGUUCAGGCCA
3673	GGCCUGAACCCACCCGAAUG	8427	CAUUCGGGUUGGUUCAGGCC
3674	GCCUGAACCCACCCGAAUGU	8428	ACAUCGGGUUGGUUCAGGCC
3676	CUGAACCCACCCGAAUGUGC	8430	GCACAUCGGGUUGGUUCAG
3685	CCGAAUGUGCUGGCUCUCA	8439	UGAGAGCCAGCACAUCGG
3701	UCAUUGGUUAUGUUGGCC	8455	GGCAACAUGAUACCAAUGA
3702	CAUUGGUUAUGUUGCCA	8456	UGGCAACAUGAUACCAAUG
3705	UGGUUAUGUUGGCCACCU	8459	AGGUGGCAACAUGAUACCA
3742	CUGCUGCCCUUAUGUGGCC	8496	GGCACAUAUAGGGCAGCAG

3746	UGCCCUAUUAUGGCCACGG	8500	CCGUGGCACAUUAAGGGCA
3748	CCCUAUUAUGGCCACGGUG	8502	CACCGUGGCACAUUAAGGG
3749	CCUAUAUGUGCCACGGUGA	8503	UCACCGUGGCACAUUAAGG
3750	CUAUUAUGGCCACGGUGAC	8504	GUACCGUGGCACAUUAAG
3751	UAUAUGUGCCACGGUGACC	8505	GGUCACCGUGGCACAUUA
3752	AUAUGUGCCACGGUGACCU	8506	AGGUCACCGUGGCACAUUA
3755	UGUGCCACGGUGACCUGCU	8509	AGCAGGUCACCGUGGCACA
3756	GUGCCACGGUGACCUGCU	8510	GAGCAGGUCACCGUGGCAC
3762	CGGUGACCUUGCUCCAGUUC	8516	GAACUGGAGCAGGUCACCG
3770	UGCUCAGUUAUCCGCU	8524	GAGCGGAUGAACUGGAGCA
3771	GCUCAGUUAUCCGCU	8525	UGAGCGGAUGAACUGGAGC
3773	UCCAGUUAUCCGCU	8527	GGUGAGCGGAUGAACUGGA
3775	CAGUUAUCCGCU	8529	GAGGUGAGCGGAUGAACUG
3777	GUUAUCCGCU	8531	CUGAGGUGAGCGGAUGAAC
3781	AUCCGCU	8535	UCCGCU
3783	CCGCU	8537	GUUCCGCU
3788	CACCU	8542	GUGGGGU
3791	CUCAGCGGAACCCACCGU	8545	ACGGUGGGGUUCCGCU
3793	CAGCGGAACCCACCGUGA	8547	UCACGGUGGGGUUCCGCU
3794	AGCGGAACCCACCGUGAA	8548	UUACCGUGGGGUUCCGCU
3795	GCGGAACCCACCGUGAAG	8549	CUUACCGUGGGGUUCCGC
3796	CGGAACCCACCGUGAAGG	8550	CCUACCGUGGGGUUCCG
3798	GAACCCACCGUGAAGGAC	8552	GUCCUACCGUGGGGUU
3799	AACCCACCGUGAAGGACC	8553	GGUCUACCGUGGGGUU
3800	ACCCACCGUGAAGGACCU	8554	AGGUCCUACCGUGGGGU
3801	CCCCACCGUGAAGGACCU	8555	GAGGUCCUACCGUGGGG
3871	AAGUUUGGCACAGGGACC	8625	GGUCCUGUGCAAAACUU
4284	GGUGGAGCAGAUAGUGUCU	9038	AGACACUAUCUGCUCCACC
4292	AGAUAGUGUCUGCACUGCU	9046	AGCAGUGCAGACACUAUCU
4308	GCUUGGGGACCAUUAUGUG	9062	CACAUAAUGGUCCCAAGC
4311	UGGGGACCAUUAUGUGCAG	9065	CUGCACAUAAUGGUCCCA
4313	GGGACCAUUAUGUGCAGCU	9067	AGCUGCACAUAAUGGUCCC
4333	CCAGCAACCUACAUGAACU	9087	AGUUCAUGUAGGUUGCUGG
4449	GCCUCCUCGGCCACUUGA	9203	UCAAGUGGGCCGAGGAGGC

[00207] The siRNAs in subset A have the following characteristics:

- Cross-reactivity: With 19mer in human *MST1R* mRNA, with 17mer/19mer in NHP *MST1R*
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species
- Off-target frequency: ≤ 20 human off-targets matched with 2 mismatches in antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF $\geq 1\%$ (pos. 2-18)

[00208] The siRNA sequences in subset A were selected for more stringent specificity to yield subset B.

Subset B includes 297 siRNAs whose base sequences are shown in **Table 4**.

Table 4. Sequences in siRNA subset B

SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
469	GCUGUGUUUGUAGCCAUAC	5223	GUAUGGCUACAAACACAGC
471	UGUGUUUGUAGCCAUACGC	5225	GCGUAUGGCUACAAACACA
472	GUGUUUGUAGCCAUACGCA	5226	UGCGUAUGGCUACAAACAC
473	UGUUUGUAGCCAUACGCAA	5227	UUGCGUAUGGCUACAAACA
474	GUUUUGUAGCCAUACGCAAU	5228	AUUGCGUAUGGCUACAAAC
475	UUUGUAGCCAUACGCAAUC	5229	GAUUGCGUAUGGCUACAAA
476	UUGUAGCCAUACGCAAUCG	5230	CGAUUGCGUAUGGCUACAA
477	UGUAGCCAUACGCAAUCGC	5231	GCGAUUGCGUAUGGCUACA

478	GUAGCCAUACGCAAUCGCC	5232	GGCGAUUGCGUAUGGCUAC
479	UAGCCAUACGCAAUCGCCU	5233	AGGCCAUUGCGUAUGGCUA
480	AGCCAUACGCAAUCGCCUG	5234	CAGGCCAUUGCGUAUGGCU
481	GCCAUACGCAAUCGCCUGC	5235	GCAGGCCAUUGCGUAUGGC
482	CCAUACGCAAUCGCCUGCA	5236	UGCAGGCCAUUGCGUAUGG
483	CAUACGCAAUCGCCUGCAU	5237	AUGCAGGCCAUUGCGUAUG
562	GGCUGCCAGACGUGUGCAG	5316	CUGCACACGUCUGGCAGCC
564	CUGCCAGACGUGUGCAGCC	5318	GGCUGCACACGUCUGGCAG
568	CAGACGUGUGCAGCCUGUG	5322	CACAGGCUGCACACGUCUG
691	UGCUCUGCAUGACCUAG	5445	CUAGGUCAUGCAGGAAGCA
692	GCUUCCUGCAUGACCUAGA	5446	UCUAGGUCAUGCAGGAAGC
693	CUUCCUGCAUGACCUAGAG	5447	CUCUAGGUCAUGCAGGAAG
717	AGGGACAGCCGUGCAUCUG	5471	CAGAUGCACGGCUGUCCCU
718	GGGACAGCCGUGCAUCUGG	5472	CCAGAUGCACGGCUGUCCC
721	ACAGCCGUGCAUCUGGCAG	5475	CUGCCAGAUGCACGGCUGU
722	CAGCCGUGCAUCUGGCAGC	5476	GCUGCCAGAUGCACGGCUG
724	GCCGUGCAUCUGGCAGCGC	5478	GCUCUGCCAGAUGCACGGC
725	CCGUGCAUCUGGCAGCGCC	5479	GGCGCUGCCAGAUGCACGG
726	CGUGCAUCUGGCAGCGCCA	5480	UGGCGCUGCCAGAUGCACG
753	CUUCUCAGCCACCAUAAC	5507	GUUAUGGUGGGCUGAGAAG
759	AGCCCAACCAUAACCGGCC	5513	GGGCCGGUUAUGGUGGGCU
761	CCCACCAUAACCGGCCCGA	5515	UCGGGCCGGUUAUGGUGGG
762	CCACCAUAACCGGCCCGAU	5516	AUCGGGCCGGUUAUGGUGG
763	CACCAUAACCGGCCCGAUG	5517	CAUCGGGCCGGUUAUGGUG
764	ACCAUAACCGGCCCGAUGA	5518	UCAUCGGGCCGGUUAUGGU
765	CCAUAACCGGCCCGAUGAC	5519	GUCAUCGGGCCGGUUAUGG
766	CAUAACCGGCCCGAUGACU	5520	AGUCAUCGGGCCGGUUAUG
767	AUAACCGGCCCGAUGACUG	5521	CAGUCAUCGGGCCGGUUAU
775	CCCGAUGACUGCCCCGACU	5529	AGUCGGGGCAGUCAUCGGG
776	CCGAUGACUGCCCCGACUG	5530	CAGUCGGGGCAGUCAUCGG
777	CGAUGACUGCCCCGACUGU	5531	ACAGUCGGGGCAGUCAUCG
801	CAGCCCAUUGGGCACCCGU	5555	ACGGGUGCCCAUUGGGCUG
804	CCCAUUGGGCACCCGUGUA	5558	UACACGGGUGCCCAUUGGG
826	GUGGUUGAGCAAGGCCAGG	5580	CCUGGCCUUGCUCAACCAC
842	AGGCCUCCUAUUUCUACGU	5596	ACGUAGAAUAGGAGGCCU
845	CCUCCUAUUUCUACGUGGC	5599	GCCACGUAGAAUAGGAGG
854	UCUACGUGGCAUCCUCACU	5608	AGUGAGGAUGCCACGUAGA
855	CUACGUGGCAUCCUCACUG	5609	CAGUGAGGAUGCCACGUAG
863	CAUCCUCACUGGACGCAGC	5617	GCUCGUGCAGUGAGGAUG
866	CCUCACUGGACGCAGCCGU	5620	ACGGCUGCUGCCAGUGAGG
895	UUCAGCCCACGCUCAGUGU	5649	ACACUGAGCGUGGGCUGAA
897	CAGCCCACGCUCAGUGUCU	5651	AGACACUGAGCGUGGGCUG
898	AGCCACGCUCAGUGUCUA	5652	UAGACACUGAGCGUGGGCU
899	GCCCACGCUCAGUGUCUAU	5653	AUAGACACUGAGCGUGGGC
900	CCCACGCUCAGUGUCUAUC	5654	GAUAGACACUGAGCGUGGG
901	CCACGCUCAGUGUCUAUCA	5655	UGAUAGACACUGAGCGUGG
903	ACGCUCAGUGUCUAUCAGG	5657	CCUGAUAGACACUGAGCGU
904	CGCUCAGUGUCUAUCAGGC	5658	GCCUGAUAGACACUGAGCG
907	UCAGUGUCUAUCAGGCUGC	5661	GACGCCUGAUAGACACUGA
908	CAGUGUCUAUCAGGCUGUCU	5662	AGACGCCUGAUAGACACUG
909	AGUGUCUAUCAGGCUGUC	5663	GAGACGCCUGAUAGACACU
910	GUGUCUAUCAGGCUGUCA	5664	UGAGACGCCUGAUAGACAC
911	UGUCUAUCAGGCUGUCAAA	5665	UUGAGACGCCUGAUAGACA
912	GUCUAUCAGGCUGUCAAG	5666	CUUGAGACGCCUGAUAGAC
913	UCUAUCAGGCUGUCAAGG	5667	CCUUGAGACGCCUGAUAGA
915	UAUCAGGCUGUCAAGGCU	5669	AGCCUUGAGACGCCUGAUA
966	GUUGUCAGUGCUGCCCAAG	5720	CUUGGGCAGCACUGACAAC
976	CUGCCCAAGCAUCUUGUCU	5730	AGACAAAGAUUCUUGGGCAG
977	UGCCCAAGCAUCUUGUCUC	5731	GAGACAAGAUUCUUGGGCA
985	CAUCUUGUCUCCUACAGUA	5739	UACUGUAGGAGACAAGAUG
986	AUCUUGUCUCCUACAGUAU	5740	AUACUGUAGGAGACAAGAUG

992	UCUCCUACAGUAUUGAAUA	5746	UAUCAAUACUGUAGGAGA
1001	GUAUUGAAUACGUGCACAG	5755	CUGUGCACGUAUUCAAUAC
1003	AUUGAAUACGUGCACAGCU	5757	AGCUUGGCACGUAUCAAU
1004	UUGAAUACGUGCACAGCUU	5758	AAGCUGUGCACGUAAUCAA
1005	UGAAUACGUGCACAGCUUC	5759	GAAGCUUGGCACGUAUUCA
1046	UCCUGACUGUACAGCCGGC	5800	GCCGGCUGUACAGUCAGGA
1048	CUGACUGUACAGCCGGCCA	5802	UGGCCGGCUGUACAGUCAG
1049	UGACUGUACAGCCGGCCAG	5803	CUGGCCGGCUGUACAGUCA
1050	GACUGUACAGCCGGCCAGC	5804	GCUGGCCGGCUGUACAGUC
1051	ACUGUACAGCCGGCCAGCG	5805	CGCUGGCCGGCUGUACAGU
1053	UGUACAGCCGGCCAGCGUG	5807	CACGCGGCCGGCUGUACA
1054	GUACAGCCGGCCAGCGUGA	5808	UCACGCGGCCGGCUGUAC
1055	UACAGCCGGCCAGCGUGAC	5809	GUCACGCGGCCGGCUGUA
1111	CUUAGCGCCACUGAGCCAG	5865	CUGGCUAGUGGCGCUAAG
1129	GAGUUGGGUGACUAUCGGG	5883	CCCGAUAGUCACCCAACUC
1130	AGUUGGGUGACUAUCGGGA	5884	UCCCGAUAGUCACCCAACU
1131	GUUGGGUGACUAUCGGGAG	5885	CUCCCGAUAGUCACCCAAC
1132	UUGGGUGACUAUCGGGAGC	5886	GCUCCCGAUAGUCACCCA
1134	GGGUGACUAUCGGGAGCUG	5888	CAGCUCCGAUAGUCACCC
1137	UGACUAUCGGGAGCUGGUC	5891	GACCAGCUCCGAUAGUCA
1138	GACUAUCGGGAGCUGGUCC	5892	GGACCAGCUCCGAUAGUC
1139	ACUAUCGGGAGCUGGUCCU	5893	AGGACCAGCUCCGAUAGU
1146	GGAGCUGGUCCUCGACUGC	5900	GCAGUCGAGGACCAGCUCC
1147	GAGCUGGUCCUCGACUGCA	5901	UGCAGUCGAGGACCAGCUC
1152	GGUCCUCGACUGCAGAUUU	5906	AAAUUCGACGUCGAGGACC
1153	GUCCUCGACUGCAGAUUUG	5907	CAAAUCGACGUCGAGGAC
1154	UCCUCGACUGCAGAUUUGC	5908	GCAAAUCGACGUCGAGGA
1155	CCUCGACUGCAGAUUUGCU	5909	AGCAAAUCGACGUCGAGG
1156	CUCGACUGCAGAUUUGCUC	5910	GAGCAAAUCGACGUCGAG
1157	UCGACUGCAGAUUUGCUCC	5911	GGAGCAAAUCGACGUCGA
1158	CGACUGCAGAUUUGCUCCA	5912	UGGAGCAAAUCGACGUCG
1161	CUGCAGAUUUGCUCCAAAA	5915	UUUUUGGAGCAAAUCGUCAG
1162	UGCAGAUUUGCUCCAAAAC	5916	GUUUUGGAGCAAAUCUGCA
1164	CAGAUUUGCUCCAAAACGC	5918	GCGUUUUGGAGCAAAUCUG
1165	AGAUUUGCUCCAAAACGCA	5919	UGCGUUUUGGAGCAAAUCU
1166	GAUUUGCUCCAAAACGCAG	5920	CUGCGUUUUGGAGCAAAUC
1170	UGCUCAAAACGCAGGCGC	5924	GCGCCUGCGUUUUGGAGCA
1171	GCUCAAAACGCAGGCGCC	5925	GGCGCCUGCGUUUUGGAGC
1172	CUCCAAAACGCAGGCGCCG	5926	CGGCGCCUGCGUUUUGGAG
1173	UCCAAAACGCAGGCGCCGG	5927	CCGGCGCCUGCGUUUUGGA
1204	GGCGGACAGCCCUACCCUG	5958	CAGGGUAGGGCUGUCCGCC
1350	CAACUCUGUCGUCUGUGCC	6104	GGCACAGACGACAGAGUUG
1405	GGUGUGGAGCGCUGUUGUG	6159	CACAACAGCGCUCCACACC
1406	GUGUGGAGCGCUGUUGUGA	6160	UCACAACAGCGCUCCACAC
1408	GUGGAGCGCUGUUGUGAAU	6162	AUUCACAACAGCGCUCCAC
1409	UGGAGCGCUGUUGUGAAUC	6163	GAUUCACAACAGCGCUCCA
1411	GAGCGCUGUUGUGAAUCC	6165	GGGAUUCACAACAGCGCUC
1443	CCUCGCGCAGGCCUCGAC	6197	GUCGAGGCCUCGCCGGAGG
1444	CUCCGCGCAGGCCUCGACU	6198	AGUCGAGGCCUCGCCGGAG
1445	UCCGCGCAGGCCUCGACUU	6199	AAGUCGAGGCCUCGCCGGA
1446	CCGCGCAGGCCUCGACUUC	6200	GAAGUCGAGGCCUCGCCGG
1447	CGGCAGGCCUCGACUUCU	6201	AGAAUCGAGGCCUCGCCG
1476	CAGUUUUUGCCCCAACCCG	6230	CGGGUUGGGGCAAAAACUG
1857	GACCUGUGGGCGUUGCCUA	6611	UAGGCAACGCCACAGGUC
1858	ACCUUGUGGGCGUUGCCUAA	6612	UUAGGCAACGCCACAGGU
1862	GUGGGCGUUGCCUAAGGGC	6616	GCCCUUAGGCAACGCCAC
1863	UGGGCGUUGCCUAAGGGCA	6617	UGCCCUUAGGCAACGCCCA
1969	CCUAAGCUUACUGAGUUC	6723	GGAACUCAGUAAGCUUAGG
2125	AAGGACAGCUAAAACUCA	6879	UGAGUUUUGAGCUGUCCUU
2142	CAGACCAGUGCCCCGGAAA	6896	UUUCCGGGGCACUGGUUCG
2143	AGACCAGUGCCCCGGAAAG	6897	CUUCCGGGGCACUGGUUCU

2144	GACCAGUGCCCCGGAAAGA	6898	UCUUUCCGGGGCACUGGUC
2148	AGUGCCCCGGAAAGACUUU	6902	AAAGUCUUUCCGGGGCACU
2149	GUGCCCCGGAAAGACUUUG	6903	CAAAGUCUUUCCGGGGCAC
2150	UGCCCCGGAAAGACUUUGU	6904	ACAAAGUCUUUCCGGGGCA
2151	GCCCCGGAAAGACUUUGUA	6905	UACAAAGUCUUUCCGGGGC
2152	CCCCGGAAAGACUUUGUAG	6906	CUACAAAGUCUUUCCGGGG
2153	CCCGGAAAGACUUUGUAGA	6907	UCUACAAAGUCUUUCCGGG
2154	CCGGAAAGACUUUGUAGAG	6908	CUCUACAAAGUCUUUCCGG
2208	GGCAGUGGGGGCCUACCAAC	6962	GUUGGUAGGCCCCACUGCC
2226	CGUCAGCCUCACCGUGACU	6980	AGUCACGGUGAGGCUGACG
2228	UCAGCCUCACCGUGACUAA	6982	UUAGUCACGGUGAGGCUGA
2229	CAGCCUCACCGUGACUAAC	6983	GUUAGUCACGGUGAGGCUG
2230	AGCCUCACCGUGACUAACA	6984	UGUUAGUCACGGUGAGGCU
2232	CCUCACCGUGACUAACAUG	6986	CAUGUUAGUCACGGUGAGG
2233	CUCACCGUGACUAACAUGC	6987	GCAUGUUAGUCACGGUGAG
2234	UCACCGUGACUAACAUGCC	6988	GGCAUGUUAGUCACGGUGA
2235	CACCGUGACUAACAUGCCA	6989	UGGCAUGUUAGUCACGGUG
2237	CCGUGACUAACAUGCCACC	6991	GGUGGCAUGUUAGUCACGG
2240	UGACUAACAUGCCACCGGG	6994	CCCGGUGGCAUGUUAGUCA
2241	GACUAACAUGCCACCGGGC	6995	GCCCGGUGGCAUGUUAGUC
2242	ACUAACAUGCCACCGGGCA	6996	UGCCCGGUGGCAUGUUAGU
2243	CUAACAUGCCACCGGGCAA	6997	UUGCCCGGUGGCAUGUUAG
2244	UAACAUGCCACCGGGCAAG	6998	CUUGCCCGGUGGCAUGUUA
2245	AACAUGCCACCGGGCAAGC	6999	GCUUGCCCGGUGGCAUGUU
2246	ACAUGCCACCGGGCAAGCA	7000	UGCUUGCCCGGUGGCAUGU
2252	CACCGGGCAAGCACUUCGG	7006	CGGAAGUCUUGCCCGGUG
2253	ACCGGGCAAGCACUUCGG	7007	CCGGAAGUCUUGCCCGGU
2257	GGCAAGCACUUCGGGUAG	7011	CUACCCGGAAGUCUUGCC
2258	GCAAGCACUUCGGGUAGA	7012	UCUACCCGGAAGUCUUGC
2259	CAAGCACUUCGGGUAGAC	7013	GUUACCCGGAAGUCUUG
2263	CACUUCGGGUAGACGGCA	7017	UGCCGUUACCCGGAAGUG
2264	ACUUCGGGUAGACGGCAC	7018	GUGCCGUCUACCCGGAAGU
2265	CUUCGGGUAGACGGCACC	7019	GGUGCCGUUACCCGGAAG
2266	UUCCGGGUAGACGGCACCU	7020	AGGUGCCGUCUACCCGGA
2267	UCCGGGUAGACGGCACCU	7021	GAGGUGCCGUUACCCGGA
2269	CGGGUAGACGGCACCUCC	7023	CGGAGGUGCCGUUACCCG
2318	UGCUGAUAGCAGUGCAACC	7072	GGUUGCACUGCUAUCAGCA
2319	GCUGAUAGCAGUGCAACCC	7073	GGGUUGCACUGCUAUCAGC
2320	CUGAUAGCAGUGCAACCCC	7074	GGGGUUGCACUGCUAUCAG
2322	GAUAGCAGUGCAACCCUC	7076	GAGGGGUUGCACUGCUAUC
2332	CAACCCUCUUGGCCCAC	7086	GUGGGCCAAAGAGGGGUUG
2366	GUCUCACUCUUGAAGGCCA	7120	UGGCCUUAAGAGUGAGAC
2369	UCACUCUUGAAGGCCAGAG	7123	CUCUGGCCUUAAGAGUGA
2386	AGUCUGUCUGUAGGCACCA	7140	UGGUGCCUACAGACAGACU
2413	GUGCUGGUCAAUGGGACUG	7167	CAGUCCCAUUGACCAGCAC
2418	GGUCAUUGGGACUGAGUGU	7172	ACACUCAGUCCCAUUGACC
2420	UCAAUUGGGACUGAGUGUCU	7174	AGACACUCAGUCCCAUUGA
2421	CAAUGGGACUGAGUGUCUG	7175	CAGACACUCAGUCCCAUUG
2422	AAUGGGACUGAGUGUCUGC	7176	GCAGACACUCAGUCCCAU
2425	GGGACUGAGUGUCUGCUAG	7179	CUAGCAGACACUCAGUCCC
2427	GACUGAGUGUCUGCUAGCA	7181	UGCUAGCAGACACUCAGUC
2430	UGAGUGUCUGCUAGCACGG	7184	CCGUGCUAGCAGACACUCA
2432	AGUGUCUGCUAGCACGGGU	7186	ACCCGUGCUAGCAGACACU
2435	GUCUGCUAGCACGGGUCAG	7189	CUGACCCGUGCUAGCAGAC
2437	CUGCUAGCACGGGUCAGUG	7191	CACUGACCCGUGCUAGCAG
2438	UGCUAGCACGGGUCAGUGA	7192	UCACUGACCCGUGCUAGCA
2440	CUAGCACGGGUCAGUGAGG	7194	CCUCACUGACCCGUGCUAG
2443	GCACGGGUCAGUGAGGGGC	7197	GCCCCUCACUGACCCGUGC
2445	ACGGGUCAGUGAGGGGCAG	7199	CUGCCCCUCACUGACCCGU
2455	GAGGGGCAGCUUUUAUGUG	7209	CACAUAAAAGCUGCCCCUC
2460	GCAGCUUUUAUGUGCCACA	7214	UGUGGCACAUAAAAGCUGC

2462	AGCUUUUAUGUGCCACACC	7216	GGUGUGGCACAUAAAAGCU
2566	GAAGACCCUGUCGUGCUAA	7320	UUAGCACGACAGGGUCUUC
2567	AAGACCCUGUCGUGCUAAG	7321	CUUAGCACGACAGGGUCUU
2571	CCUGUCGUGCUAAGCAUC	7325	GAUGCUUAGCACGACAGG
2572	CCUGUCGUGCUAAGCAUCA	7326	UGAUGCUUAGCACGACAGG
2575	GUCGUGCUAAGCAUCAGCC	7329	GGCUGAUGCUUAGCACGAC
2577	CGUGCUAAGCAUCAGCCCC	7331	GGGGCUGAUGCUUAGCACG
2581	CUAAGCAUCAGCCCCAACU	7335	AGUUGGGGCUGAUGCUUAG
2582	UAAGCAUCAGCCCCAACUG	7336	CAGUUGGGGCUGAUGCUUA
2628	CUGUGGCCAGCAUCUAACU	7382	AGUUAGAUGCUGGCCACAG
2629	UGUGGCCAGCAUCUAACUU	7383	AAGUUAGAUGCUGGCCACA
2644	ACUUCAGCAUGGCACUUAAG	7398	CUAAGUGCCAUGCUGAAGU
2646	UUCAGCAUGGCACUUAAGUG	7400	CACUAAAGUGCCAUGCUGAA
2648	CAGCAUGGCACUUAAGUGCU	7402	AGCACUAAAGUGCCAUGCUG
2652	AUGGCACUUAAGUGCUGUCA	7406	UGACAGCACUAAAGUGCCA
2655	GCACUUAAGUGCUGUCAUUC	7409	GAAUGACAGCACUAAAGUGC
2656	CACUUAAGUGCUGUCAUUC	7410	GGAAUGACAGCACUAAAGUG
2661	AGUGCUGUCAUUCUAGAC	7415	GUCAUGGAAUGACAGCACU
2663	UGCUGUCAUUCUAGACGG	7417	CCGUCUUGGAAUGACAGCA
2664	GCUGUCAUUCUAGACGGG	7418	CCCGUCAUGGAAUGACAGC
2666	UGUCAUUCUAGACGGGCU	7420	AGCCCGUCAUGGAAUGACA
2668	UCAUUCUAGACGGGCUUA	7422	UAAGCCCGUCAUGGAAUGA
2669	CAUUCUAGACGGGCUUAG	7423	CUAAGCCCGUCAUGGAAUG
2670	AUUCUAGACGGGCUUAGG	7424	CCUAAGCCCGUCAUGGAAU
2671	UUUCUAGACGGGCUUAGG	7425	CCCUAAGCCCGUCAUGGAA
2673	CCAUGACGGGCUUAGGGCA	7427	UGCCCUAAGCCCGUCAUGG
2676	UGACGGGCUUAGGGCAGUG	7430	CACUGCCCUAAGCCCGUCA
2678	ACGGGCUUAGGGCAGUGGA	7432	UCCACUGCCCUAAGCCCGU
2891	AGGAGCAUGCCAUAAGUU	7645	AACUUAAGGCAUGCUCCU
3084	UAUCCUGGGUAGAGUGUG	7838	CACCACUCUACCCAGGAUA
3186	UGCACUGGUCUUCAGCUAC	7940	GUAGCUGAAGACCAGUGCA
3191	UGGUCUUCAGCUACUGGUG	7945	CACCAGUAGCUGAAGACCA
3192	GGUCUUCAGCUACUGGUGG	7946	CCACCAGUAGCUGAAGACC
3223	CUAGUUCUUCUCCCAACC	7977	GGUUGGGAGGAAGAACUAG
3279	CACACCCUGCCUAUUCUG	8033	CAGAAUAGGCAGGGGUGUG
3297	GUACUGGGCUCUGACUAC	8051	GUAGUCAGAGCCCAGUAC
3298	UACUCGGGCUUGACUACA	8052	UGUAGUCAGAGCCCAGUA
3299	ACUCGGGCUUGACUACAG	8053	CUGUAGUCAGAGCCCAGU
3300	CUCGGGCUUGACUACAGA	8054	UCUGUAGUCAGAGCCCAG
3301	UCGGGCUUGACUACAGAA	8055	UUUCUGUAGUCAGAGCCCAG
3560	GAGAAUACAUAGACCAGGC	8314	GCCUGGUCUAUGUAUUCUC
3563	AAUACAUAGACCAGGCCCA	8317	UGGGCCUGGUCUAUGUAU
3564	AUACAUAGACCAGGCCAG	8318	CUGGGCCUGGUCUAUGUAU
3568	AUAGACCAGGCCAGAAUC	8322	GAUUCUGGGCCUGGUCUAU
3570	AGACCAGGCCAGAAUCGA	8324	UCGAUUCUGGGCCUGGUCU
3574	CAGGCCAGAAUCGAAUCC	8328	GGAUUCGAUUCUGGGCCUG
3576	GGCCAGAAUCGAAUCCAA	8330	UUUGGAUUCGAUUCUGGGC
3577	GCCCAGAAUCGAAUCCAAU	8331	AUUGGAUUCGAUUCUGGGC
3578	CCCAGAAUCGAAUCCAAUG	8332	CAUUGGAUUCGAUUCUGGG
3580	CAGAAUCGAAUCCAAUGUG	8334	CACAUUGGAUUCGAUUCUG
3581	AGAAUCGAAUCCAAUGUGC	8335	GCACAUUGGAUUCGAUUCU
3582	GAAUCGAAUCCAAUGUGCC	8336	GGCACAUUGGAUUCGAUUC
3583	AAUCGAAUCCAAUGUGCCA	8337	UGGCACAUUGGAUUCGAU
3584	AUCGAAUCCAAUGUGCCA	8338	AUGGCACAUUGGAUUCGAU
3586	CGAAUCCAAUGUGCCAUA	8340	UGAUGGCACAUUGGAUUCG
3587	GAAUCCAAUGUGCCAUA	8341	UUUGAUGGCACAUUGGAUUC
3588	AAUCCAAUGUGCCAUAAG	8342	CUUGAUGGCACAUUGGAUUC
3592	CAUUGUGCCAUAAGUCAC	8346	GUGACUUGAUGGCACAUUG
3594	AUGUGCCAUAAGUCACUA	8348	UAGUGACUUGAUGGCACAU
3595	UGUGCCAUAAGUCACUAA	8349	UUAGUGACUUGAUGGCACA
3596	GUGCCAUAAGUCACUAAAG	8350	CUUAGUGACUUGAUGGCAC

3597	UGCCAUCAAGUCACUAAGU	8351	ACUUGAGUGACUUGAUGGCA
3600	CAUCAAGUCACUAAGUCGC	8354	GCGACUUGAGUACUUGAUG
3655	GAGGGGCGUCUACUGCGUG	8409	CACGCAUGAGCAGCCCCUC
3656	AGGGGCGUCUACUGCGUGG	8410	CCACGCAUGAGCAGCCCCU
3657	GGGGCGUCUACUGCGUGGC	8411	GCCACGCAUGAGCAGCCCC
3659	GGCUGCUACUGCGUGGCCU	8413	AGGCCACGCAUGAGCAGCC
3666	CAUGCGUGGCCUGAACCCAC	8420	GUGGUUCAGGCCACGCAUG
3671	GUGGCCUGAACCCACCCGAA	8425	UUCGGGUGGUUCAGGCCAC
3672	UGGCCUGAACCCACCCGAAU	8426	AUUCGGGUGGUUCAGGCCA
3673	GGCCUGAACCCACCCGAAUG	8427	CAUUCGGGUGGUUCAGGCC
3674	GCCUGAACCCACCCGAAUGU	8428	ACAUUCGGGUGGUUCAGGC
3676	CUGAACCCACCCGAAUGUGC	8430	GCACAUUCGGGUGGUUCAG
3685	CCGAUUGUGCUGGCUCUCA	8439	UGAGAGCCAGCACAUUCGG
3701	UCAUUGGUAUCAUGUUGCC	8455	GGCAACAUGAUACCAAUGA
3702	CAUUGGUAUCAUGUUGCCA	8456	UGGCAACAUGAUACCAAUG
3705	UGGUAUCAUGUUGCCACCU	8459	AGGUGGCAACAUGAUACCA
3746	UGCCCUAUAUGUGCCACGG	8500	CCGUGGCACAUUAAGGGCA
3748	CCCUAUAUGUGCCACGGUG	8502	CACCGUGGCACAUUAAGGG
3749	CCUAUAUGUGCCACGGUGA	8503	UCACCGUGGCACAUUAAGG
3750	CUAUAUGUGCCACGGUGAC	8504	GUCACCGUGGCACAUUAAG
3751	UAUAUGUGCCACGGUGACC	8505	GGUCACCGUGGCACAUUA
3752	AUAUGUGCCACGGUGACCU	8506	AGGUCACCGUGGCACAUUA
3755	UGUGCCACGGUGACCUGCU	8509	AGCAGGUCACCGUGGCACA
3762	CGGUGACCUGCUCCAGUUC	8516	GAACUGGAGCAGGUCACCG
3770	UGCUCACAGUUCAUCCGCUC	8524	GAGCGGAUGAACUGGAGCA
3771	GCUCACAGUUCAUCCGCUCA	8525	UGAGCGGAUGAACUGGAGC
3773	UCCAGUUCAUCCGCUCACC	8527	GGUGAGCGGAUGAACUGGA
3775	CAGUUCAUCCGCUCACCUC	8529	GAGGUGAGCGGAUGAACUG
3777	GUUCAUCGCUCACCUCAG	8531	CUGAGGUGAGCGGAUGAAC
3783	CCGCUCACCUCAGCGGAAC	8537	GUUCCGCUGAGGUGAGCGG
3788	CACCUCAGCGGAACCCAC	8542	GUGGGGUUCCGCUGAGGUG
3791	CUCAGCGGAACCCACCGU	8545	ACGGUGGGGUUCCGCUGAG
3793	CAGCGGAACCCACCGUGA	8547	UCACGGUGGGGUUCCGCUG
3794	AGCGGAACCCACCGUGAA	8548	UUCACGGUGGGGUUCCGCU
3795	GCGGAACCCACCGUGAAG	8549	CUUCACGGUGGGGUUCCGC
3798	GAACCCACCGUGAAGGAC	8552	GUCCUUCACGGUGGGGUUC
3799	AACCCACCGUGAAGGACC	8553	GGUCUUCACGGUGGGGUU
3800	ACCCACCGUGAAGGACCU	8554	AGGUCCUUCACGGUGGGGU
3871	AAGUUUGUGCACAGGGACC	8625	GGUCCUGUGCACAACUUC
4284	GGUGGAGCAGAUAGUGUCU	9038	AGACACUAUCUGCUCCACC
4292	AGAUAGUGUCUGCACUGCU	9046	AGCAGUGCAGACACUAUCU
4308	GCUUGGGGACCAUUAUGUG	9062	CACAUAAUGGUCCCCAAGC
4311	UGGGGACCAUUAUGUGCAG	9065	CUGCACAUAAUGGUCCCCA
4313	GGGACCAUUAUGUGCAGCU	9067	AGCUGCACAUAAUGGUCCC
4333	CCAGCAACCUACAUGAACU	9087	AGUUCAUAGGUUGCUGG

[00209] The siRNAs in subset B have the following characteristics:

- Cross-reactivity: With 19mer in human *MST1R* mRNA, with 17mer/19mer in NHP *MST1R*
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species
- Off-target frequency: ≤15 human off-targets matched with 2 mismatches in antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[00210] The siRNA sequences in subset B were further selected for absence of seed regions in the AS strand that are identical to a seed region of known human miRNA to yield subset C. Subset C includes 184 siRNAs whose base sequences are shown in **Table 5**.

Table 5. Sequences in siRNA subset C

SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
471	UGUGUUUGUAGCCAUACGC	5225	GCGUAUGGCUACAAACACA
472	GUGUUUGUAGCCAUACGCA	5226	UGCGUAUGGCUACAAACAC
473	UGUUUGUAGCCAUACGCAA	5227	UUGCGUAUGGCUACAAACA
474	GUUUGUAGCCAUACGCAAU	5228	AUUGCGUAUGGCUACAAAC
475	UUUGUAGCCAUACGCAAUC	5229	GAUUGCGUAUGGCUACAAA
476	UUGUAGCCAUACGCAAUCG	5230	CGAUUGCGUAUGGCUACAA
477	UGUAGCCAUACGCAAUCGC	5231	GCGAUUGCGUAUGGCUACA
478	GUAGCCAUACGCAAUCGCC	5232	GGCGAUUGCGUAUGGCUAC
480	AGCCAUACGCAAUCGCCUG	5234	CAGGCGAUUGCGUAUGGCU
482	CCAUACGCAAUCGCCUGCA	5236	UGCAGGCGAUUGCGUAUGG
562	GGCUGCCAGACGUGUGCAG	5316	CUGCACACGUCUGGCAGCC
564	CUGCCAGACGUGUGCAGCC	5318	GGCUGCACACGUCUGGCAG
691	UGCUCUCCUGCAUGACCUAG	5445	CUAGGUCAUGCAGGAAGCA
692	GCUUCCUGCAUGACCUAGA	5446	UCUAGGUCAUGCAGGAAGC
693	CUUCCUGCAUGACCUAGAG	5447	CUUAGGUCAUGCAGGAAG
717	AGGGACAGCCGUGCAUCUG	5471	CAGAUGCACGGCUGUCUCCU
724	GCCGUGCAUCUGGCAGCGC	5478	GCGCUGCCAGAUGCACGGC
725	CCGUGCAUCUGGCAGCGCC	5479	GGCGCUGCCAGAUGCACGG
726	CGUGCAUCUGGCAGCGCCA	5480	UGGCGCUGCCAGAUGCACG
753	CUUCUCAGCCACCAUAAC	5507	GUUAUGGUGGGCUGAGAAG
763	CACCAUAACCGGCCCGAUG	5517	CAUCGGGCCCGGUUAUGGUG
764	ACCAUAACCGGCCCGAUGA	5518	UCAUCGGGCCCGGUUAUGGU
765	CCAUAACCGGCCCGAUGAC	5519	GUCAUCGGGCCCGGUUAUGG
766	CAUAACCGGCCCGAUGACU	5520	AGUCAUCGGGCCCGGUUAUG
767	AUAACCGGCCCGAUGACUG	5521	CAGUCAUCGGGCCCGGUUAU
775	CCCGAUGACUGCCCGACU	5529	AGUCGGGGCAGUCAUCGGG
776	CCGAUGACUGCCCGACUG	5530	CAGUCGGGGCAGUCAUCGG
777	CGAUGACUGCCCGACUGU	5531	ACAGUCGGGGCAGUCAUCG
801	CAGCCCAUUGGGCACCUGU	5555	ACGGGUGCCCAAUGGGCUG
842	AGGCCUCCUAUUUCUACGU	5596	ACGUAGAAAUAGGAGGCCU
845	CCUCCUAUUUCUACGUGGC	5599	GCCACGUAGAAAUAGGAGG
895	UUCAGCCACGCUCAGUGU	5649	ACACUGAGCGUGGGCUGAA
898	AGCCACGCUAGUGUCUA	5652	UAGACACUGAGCGUGGGCU
899	GCCACGCUAGUGUCUAU	5653	AUAGACACUGAGCGUGGGC
900	CCCACGCUAGUGUCUAUC	5654	GAUAGACACUGAGCGUGGG
901	CCACGCUAGUGUCUAUCA	5655	UGAUAGACACUGAGCGUGG
903	ACGCUAGUGUCUAUCAGG	5657	CCUGAUAGACACUGAGCGU
904	CGCUAGUGUCUAUCAGGC	5658	GCCUGAUAGACACUGAGCG
907	UCAGUGUCUAUCAGGCUC	5661	GACGCCUGAUAGACACUGA
909	AGUGUCUAUCAGGCUCUC	5663	GAGACGCCUGAUAGACACU
910	GUGUCUAUCAGGCGUCUA	5664	UGAGACGCCUGAUAGACAC
912	GUCUAUCAGGCGUCUAAG	5666	CUUGAGACGCCUGAUAGAC
913	UCUAUCAGGCGUCUAAGG	5667	CCUUGAGACGCCUGAUAGA
966	GUUGUCAGUGCUGCCCAAG	5720	CUUGGGCAGCACUGACAAC
976	CUGCCCAAGCAUCUUGUCU	5730	AGACAAGAUUCUUGGGCAG
977	UGCCCAAGCAUCUUGUCUC	5731	GAGACAAGAUUCUUGGGCA
1001	GUUUGAAUACGUGCACAG	5755	CUGUGCACGUUUUCAAUAC
1003	AUUGAAUACGUGCACAGCU	5757	AGCUGGCACGUUUUCAAU
1004	UUGAAUACGUGCACAGCUU	5758	AAGCUGGCACGUUUUCAA
1046	UCCUGACUGUACAGCCGGC	5800	GCCGGCUGUACAGUCAGGA
1049	UGACUGUACAGCCGGCCAG	5803	CUGGCCGGCUGUACAGUCA
1053	UGUACAGCCGGCCAGCGUG	5807	CACGUCGGCCGGCUGUACA
1054	GUACAGCCGGCCAGCGUGA	5808	UCACGUCGGCCGGCUGUAC
1055	UACAGCCGGCCAGCGUGAC	5809	GUACGUCGGCCGGCUGUA
1129	GAGUUGGGUGACUAUCGGG	5883	CCCGAUAGUCACCCAAUC
1130	AGUUGGGUGACUAUCGGGA	5884	UCCCGAUAGUCACCCAAUC
1131	GUUGGGUGACUAUCGGGAG	5885	CUCCCGAUAGUCACCCAAAC
1132	UUGGGUGACUAUCGGGAGC	5886	GCUCCCGAUAGUCACCCAA

1134	GGGUGACUAUCGGGAGCUG	5888	CAGCUCCTCGAUAGUCACCC
1138	GACUAUCGGGAGCUGGUCC	5892	GGACCAGCUCCTCGAUAGUC
1146	GGAGCUGGUCUCGACUGC	5900	GCAGUCGAGGACCAGCUC
1147	GAGCUGGUCCUCGACUGCA	5901	UGCAGUCGAGGACCAGCUC
1152	GGUCCUCGACUGCAGAUUU	5906	AAAUUCGAGCUCGAGGACC
1153	GUCCUCGACUGCAGAUUUG	5907	CAAAUCUGCAGUCGAGGAC
1155	CCUCGACUGCAGAUUUGCU	5909	AGCAAAUCUGCAGUCGAGG
1157	UCGACUGCAGAUUUGCUC	5911	GGAGCAAAUCUGCAGUCGA
1162	UGCAGAUUUGCUCCAAAAC	5916	GUUUUGGAGCAAAUCUGCA
1164	CAGAUUUGCUCCAAAACGC	5918	CGGUUUUGGAGCAAAUCUG
1166	GAUUUGCUCCAAAACGCAG	5920	CUGCGUUUUUGGAGCAAAUC
1173	UCCAAAACGCAGGCGCCGG	5927	CCGGCGCCUGCGUUUUUGGA
1350	CAACUCUGUCGUCGUGGCC	6104	GGCACAGACGACAGAGUUG
1408	GUGGAGCGCUGUUGUGAAU	6162	AUUCACAACAGCGCUCCAC
1409	UGGAGCGCUGUUGUGAAUC	6163	GAUUCACAACAGCGCUCCA
1443	CCUCCGGCGAGGCCUCGAC	6197	GUUCGAGGCCUCGCCGGAGG
1444	CUCCGGCGAGGCCUCGACU	6198	AGUCGAGGCCUCGCCGGAG
1445	UCCGGCGAGGCCUCGACUU	6199	AAGUCGAGGCCUCGCCGGA
1446	CCGGCGAGGCCUCGACUUC	6200	GAAGUCGAGGCCUCGCCGG
1447	CGGCGAGGCCUCGACUUCU	6201	AGAAGUCGAGGCCUCGCCG
1857	GACCUGUGGGCGUUGCUA	6611	UAGGCAACGCCACAGGUC
1862	GUGGGCGUUGCCUAAGGGC	6616	GCCCUUAGGCAACGCCCAC
2125	AAGGACAGCUCAAAACUCA	6879	UGAGUUUUGAGCUGUCCUU
2143	AGACCAGUGCCCGGAAAG	6897	CUUUCCGGGGCACUGGUCU
2151	GCCCCGGAAAGACUUGUA	6905	UACAAAGUCUUUCCGGGGC
2154	CCGGAAAGACUUGUAGAG	6908	CUUCUACAAAGUCUUUCCGG
2208	GGCAGUGGGGCCUACCAAC	6962	GUUGGUAGGCCCCACUGCC
2226	CGUCAGCCUCACCGUGACU	6980	AGUCACGGUGAGGCUGACG
2228	UCAGCCUCACCGUGACUAA	6982	UUAGUCACGGUGAGGCUGA
2229	CAGCCUCACCGUGACUAA	6983	GUUAGUCACGGUGAGGCUG
2230	AGCCUCACCGUGACUACA	6984	UGUUAGUCACGGUGAGGCU
2232	CCUCACCGUGACUACAUG	6986	CAUGUUAGUCACGGUGAGG
2233	CUCACCGUGACUACAUGC	6987	GCAUGUUAGUCACGGUGAG
2234	UCACCGUGACUACAUGCC	6988	GGCAUGUUAGUCACGGUGA
2240	UGACUACAUGCCACCGGG	6994	CCCGGUGGCAUGUUAGUCA
2242	ACUACAUGCCACCGGGCA	6996	UGCCCGGUGGCAUGUUAGU
2243	CUAACAUGCCACCGGGCAA	6997	UUGCCCGGUGGCAUGUUAG
2244	UAACAUGCCACCGGGCAAG	6998	CUUGCCCGGUGGCAUGUUA
2245	AACAUGCCACCGGGCAAGC	6999	GCUUGCCCGGUGGCAUGUU
2252	CACCGGGCAAGCACUUCG	7006	CGGAAGUCUUGCCCGGUG
2257	GGCAAGCACUUCCGGGUAG	7011	CUACCCGGAAGUGCUUGCC
2258	GCAAGCACUUCCGGGUAGA	7012	UCUACCCGGAAGUGCUUGC
2259	CAAGCACUUCCGGGUAGAC	7013	GUUACCCGGAAGUGCUUG
2263	CACUUCCGGGUAGACGGCA	7017	UGCCGUCUACCCGGAAGUG
2264	ACUUCCGGGUAGACGGCAC	7018	GUGCCGUCUACCCGGAAGU
2265	CUUCCGGGUAGACGGCAC	7019	GGUGCCGUCUACCCGGAAG
2267	UCCGGGUAGACGGCACUC	7021	GAGGUGCCGUCUACCCGGA
2366	GUCUCACUCUUGAAGGCCA	7120	UGGCCUUAAGAGUGAGAC
2369	UCACUCUUGAAGGCCAGAG	7123	CUUCUGGCCUUAAGAGUGA
2418	GGUCAAUGGGACUGAGUGU	7172	ACACUCAGUCCAUUGACC
2421	CAAUGGGACUGAGUGUCUG	7175	CAGACACUCAGUCCAUUG
2430	UGAGUGUCUGCUAGCACGG	7184	CCGUGCUAGCAGACACUCA
2432	AGUGUCUGCUAGCACGGU	7186	ACCCGUGCUAGCAGACACU
2435	GUCUGCUAGCACGGUCAG	7189	CUGACCCGUGCUAGCAGAC
2438	UGCUGACACGGGUCAGUGA	7192	UCACUGACCCGUGCUAGCA
2445	ACGGGUCAGUGAGGGGCAG	7199	CUGCCCCUCACUGACCCGU
2455	GAGGGGCAGCUUUUAUGUG	7209	CACAUAAAAGCUGCCCCUC
2571	CCCUUGUCGUGCUAAGCAUC	7325	GAUGCUUAGCACGACAGGG
2572	CCUGUCGUGCUAAGCAUCA	7326	UGAUGCUUAGCACGACAGG
2628	CUGUGGCCAGCAUCUAACU	7382	AGUUAGAUGCUGGCCACAG
2629	UGUGGCCAGCAUCUAACUU	7383	AAGUUAGAUGCUGGCCACA

2644	ACUUCAGCAUGGCACUAG	7398	CUAAGUGCCAUGCUGAAGU
2646	UUCAGCAUGGCACUAGUG	7400	CACUAAGUGCCAUGCUGAA
2648	CAGCAUGGCACUAGUGCU	7402	AGCACUAAGUGCCAUGCUG
2655	GCACUAGUGCUUGCAUUC	7409	GAAUGACAGCACUAAGUGC
2656	CACUAGUGCUGUCAUUC	7410	GGAAUGACAGCACUAAGUG
2661	AGUGCUUGCAUUCACUAG	7415	GUCAUGGAAUGACAGCACU
2663	UGCUGCAUUCACUAGCGG	7417	CCGUCAUGGAAUGACAGCA
2664	GCUGUCAUUCACUAGCGG	7418	CCCGUCAUGGAAUGACAGC
2666	UGUCAUUCACUAGCGGCU	7420	AGCCCGUCAUGGAAUGACA
2668	UCAUUCACUAGCGGCUUA	7422	UAAGCCCGUCAUGGAAUGA
2669	CAUUCACUAGCGGCUUAG	7423	CUAAGCCCGUCAUGGAAUG
2670	AUUCACUAGCGGCUUAGG	7424	CCUAAGCCCGUCAUGGAAU
2671	UUCACUAGCGGCUUAGGG	7425	CCCUAAGCCCGUCAUGGAA
2676	UGACGGGCUUAGGGCAGUG	7430	CACUGCCCUAAGCCCGUCA
2891	AGGAGCAUGCCAUUAAGUU	7645	AACUUAAGUGCAUGCUCU
3186	UGCACUGGUCUUCAGCUAC	7940	GUAGCUGAAGACCAGUGCA
3191	UGGUCUUCAGCUACUGGUG	7945	CACCAGUAGCUGAAGACCA
3279	CACACCCUGCCUAUUCUG	8033	CAGAAUAGGCAGGGGUGUG
3297	GUACUCGGGCUUGACUAC	8051	GUAGUCAGAGCCCGAGUAC
3298	UACUCGGGCUUGACUACA	8052	UGUAGUCAGAGCCCGAGUA
3299	ACUCGGGCUUGACUACAG	8053	CUGUAGUCAGAGCCCGAGU
3560	GAGAAUACAUAGACCAGGC	8314	GCCUGGUCUAUGUAUUCUC
3570	AGACCAGGCCAGAAUCGA	8324	UCGAUUCUGGGCCUGGUCU
3574	CAGGCCAGAAUCGAAUCC	8328	GGAUUCGAUUCUGGGCCUG
3576	GGCCAGAAUCGAAUCCAA	8330	UUUGAUUCGAUUCUGGGCC
3578	CCCAGAAUCGAAUCCAAUG	8332	CAUUGGAUUCGAUUCUGGG
3580	CAGAAUCGAAUCCAAUGUG	8334	CACAUUGGAUUCGAUUCUG
3581	AGAAUCGAAUCCAAUGUGC	8335	GCACAUUGGAUUCGAUUCU
3583	AAUCGAAUCCAAUGUGCCA	8337	UGGCACAUUGGAUUCGAUU
3584	AUCGAAUCCAAUGUGCCAU	8338	AUGGCACAUUGGAUUCGAU
3586	CGAAUCCAAUGUGCCAUCA	8340	UGAUUGGCACAUUGGAUUCG
3588	AAUCCAAUGUGCCAUCAAG	8342	CUUGAUUGGCACAUUGGAUU
3592	CAAUGUGCCAUCAAGUCAC	8346	GUGACUUGAUUGGCACAUUG
3594	AUGUGCCAUCAAGUCACUA	8348	UAGUGACUUGAUUGGCACAU
3597	UGCCAUCAAGUCACUAAGU	8351	ACUUAUGACUUGAUUGGCA
3600	CAUCAAGUCACUAAGUCGC	8354	GCGACUUAUGACUUGAUG
3655	GAGGGGCGUCUAGCGUGG	8409	CACGCAUGAGCAGCCCUUC
3656	AGGGGCGUCUAGCGUGG	8410	CCACGCAUGAGCAGCCCU
3657	GGGGCGUCUAGCGUGG	8411	GCCACGCAUGAGCAGCCCC
3659	GGCGUCUAGCGUGGCCU	8413	AGGCCACGCAUGAGCAGCC
3671	GUGGCCUGAACCACCCGAA	8425	UUCGGGUGGUUCAGGCCAC
3672	UGGCCUGAACCACCCGAAU	8426	AUUCGGGUGGUUCAGGCCA
3673	GGCCUGAACCACCCGAAUG	8427	CAUUCGGGUGGUUCAGGCC
3674	GCCUGAACCACCCGAAUGU	8428	ACAUUCGGGUGGUUCAGGC
3676	CUGAACCACCCGAAUGUGC	8430	GCACAUUCGGGUGGUUCAG
3685	CCGAAUGUGCUGGCUCUCA	8439	UGAGAGCCAGCACAUCGG
3701	UCAUUGGUUAUGUUGGCC	8455	GGCAACAUGAUACCAUGA
3705	UGGUUAUGUUGGCCACCU	8459	AGGUGGCAACAUGAUACCA
3748	CCCUAUAUGUGCCACGGUG	8502	CACCGUGGCACAUAUAGGG
3749	CCUAUAUGUGCCACGGUGA	8503	UCACCGUGGCACAUAUAGG
3750	CUAUAUGUGCCACGGUGAC	8504	GUACCGUGGCACAUAUAG
3752	AUAUGUGCCACGGUGACCU	8506	AGGUCACCGUGGCACAUAU
3771	GUCCAGUUCAUCCGCUCA	8525	UGAGCGGAUGAACUGGAGC
3773	UCCAGUUCAUCCGCUCACC	8527	GGUGAGCGGAUGAACUGGA
3775	CAGUUCAUCCGCUCACCUC	8529	GAGGUGAGCGGAUGAACUG
3777	GUUCAUCCGCUCACCUCAG	8531	CUGAGGUGAGCGGAUGAAC
3793	CAGCGGAACCCACCGUGA	8547	UCACGGUGGGGUUCCGCU
3794	AGCGGAACCCACCGUGAA	8548	UUACGGUGGGGUUCCGCU
3795	GCGGAACCCACCGUGAAG	8549	CUUCACGGUGGGGUUCCGC
3799	AACCCACCGUGAAGGACC	8553	GGUCUUCACGGUGGGGUU
3800	ACCCACCGUGAAGGACCU	8554	AGGUCCUUCACGGUGGGGU

3871	AAGUUUGUGCACAGGGACC	8625	GGUCCUGUGCACAAACUU
4308	GCUUGGGGACCAUUAUGUG	9062	CACAUAAUGGUCCCAAGC
4311	UGGGGACCAUUAUGUGCAG	9065	CUGCACAUAUUGGUCCCA
4313	GGGACCAUUAUGUGCAGCU	9067	AGCUGCACAUAUUGGUCCC

[00211] The siRNAs in subset C have the following characteristics:

- Cross-reactivity: With 19mer in human *MST1R* mRNA, with 17mer/19mer in NHP *MST1R*
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤15 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[00212] The siRNA sequences in subset C were also selected for absence of seed regions in the AS or S strands that are identical to a seed region of known human miRNA to yield subset D. Subset D includes 121 siRNAs whose base sequences are shown in **Table 6**.

Table 6. Sequences in siRNA subset D

SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
471	UGUGUUUGUAGCCAUACGC	5225	GCGUAUGGCUACAAACACA
472	GUGUUUGUAGCCAUACGCA	5226	UGCGUAUGGCUACAAACAC
474	GUUUGUAGCCAUACGCAAU	5228	AUUGCGUAUGGCUACAAAC
476	UUGUAGCCAUACGCAAUCG	5230	CGAUUGCGUAUGGCUACAA
477	UGUAGCCAUACGCAAUCGC	5231	GCGAUUGCGUAUGGCUACA
480	AGCCAUACGCAAUCGCCUG	5234	CAGGCGAUUGCGUAUGGCU
482	CCAUACGCAAUCGCCUGCA	5236	UGCAGGCGAUUGCGUAUGG
692	GCUUCCUGCAUGACCUAGA	5446	UCUAGGUCAUAGCAGGAAGC
717	AGGGACAGCCGUGCAUCUG	5471	CAGAUGCACGGCUGUCCCU
726	CGUGCAUCUGGCAGCGCCA	5480	UGGCGCUGCCAGAUGCACG
753	CUUCUCAGCCCACCAUAAC	5507	GUUAUGGUGGGCUGAGAAG
763	CACCAUAACCGGCCCGAUG	5517	CAUCGGGCCCGGUUAUGGUG
764	ACCAUAACCGGCCCGAUGA	5518	UCAUCGGGCCCGGUUAUGGU
765	CCAUAACCGGCCCGAUGAC	5519	GUCAUCGGGCCCGGUUAUGG
766	CAUAACCGGCCCGAUGACU	5520	AGUCAUCGGGCCCGGUUAUG
767	AUAACCGGCCCGAUGACUG	5521	CAGUCAUCGGGCCCGGUUAU
775	CCCGAUGACUGCCCCGACU	5529	AGUCGGGGCAGUCAUCGGG
776	CCGAUGACUGCCCCGACUG	5530	CAGUCGGGGCAGUCAUCGG
777	CGAUGACUGCCCCGACUGU	5531	ACAGUCGGGGCAGUCAUCG
801	CAGCCCAUUGGGCACCUGU	5555	ACGGGUGCCCAUUGGGCUG
824	CUGUGGUUGAGCAAGGCCA	5578	UGGCCUUGCUCACCACAG
845	CCUCCUAUUUCUACGUGGC	5599	GCCACGUAGAAUAGGAGG
864	AUCCUCACUGGACGCAGCC	5618	GGCUGCGUCCAGUGAGGAU
898	AGCCACGCUCAGUGUCUA	5652	UAGACACUGAGCGUGGGCU
900	CCCACGCUCAGUGUCUAUC	5654	GAUAGACACUGAGCGUGGG
901	CCACGCUCAGUGUCUAUCA	5655	UGAUAGACACUGAGCGUGG
903	ACGCUCAGUGUCUAUCAGG	5657	CCUGAUAGACACUGAGCGU
910	GUGUCUAUCAGGCGUCUCA	5664	UGAGACGCCUGAUAGACAC
912	GUCUAUCAGGCGUCUCAAG	5666	CUUGAGACGCCUGAUAGAC
913	UCUAUCAGGCGUCUCAAGG	5667	CCUUGAGACGCCUGAUAGA
948	CGCACCGGGCUUUGUGGCG	5702	CGCCACAAAGCCCGUGGCG
966	GUUGUCAGUGCUGCCCAAG	5720	CUUGGGCAGCACUGACAAC
976	CUGCCCAAGCAUCUUGUCU	5730	AGACAAGAUGCUGGGCAG
977	UGCCCAAGCAUCUUGUCUC	5731	GAGACAAGAUGCUGGGCA
990	UGUCUCCUACAGUAUUGAA	5744	UUCAAUACUGUAGGAGACA

1001	GUUUGAAUACGUGCACAG	5755	CUGUGCACGUUUCAAUAC
1003	AUUGAAUACGUGCACAGCU	5757	AGCUUGGCACGUUUCAAU
1042	UACUCCUGACUGUACAGC	5796	GCUGUACAGUCAGGAAGUA
1046	UCCUGACUGUACAGCCGGC	5800	GCCGGCUGUACAGUCAGGA
1049	UGACUGUACAGCCGGCCAG	5803	CUGGCCGGCUGUACAGUCA
1053	UGUACAGCCGGCCAGCGUG	5807	CACGCGGCCGGCUGUACA
1054	GUACAGCCGGCCAGCGUGA	5808	UCACGCGGCCGGCUGUAC
1124	AGCCAGAGUUGGGUGACUA	5878	UAGUCACCCAAUCUUGGCU
1131	GUUGGGUGACUAUCGGGAG	5885	CUCCCGAUAGUACCCAAAC
1134	GGGUGACUAUCGGGAGCUG	5888	CAGCUCGCCGAUAGUACCC
1138	GACUAUCGGGAGCUGGUCC	5892	GGACCAGCUCGCCGAUAGUC
1147	GAGCUGGUCCUCGACUGCA	5901	UGCAGUCGAGGACCAGCUC
1153	GUCCUCGACUGCAGAUUUG	5907	CAAAUCUGCAGUCGAGGAC
1155	CCUCGACUGCAGAUUUGCU	5909	AGCAAAUCUGCAGUCGAGG
1157	UCGACUGCAGAUUUGCUCC	5911	GGAGCAAAUCUGCAGUCGA
1162	UGCAGAUUUGCUCCAAAC	5916	GUUUUGGAGCAAAUCUGCA
1164	CAGAUUUGCUCCAAACGC	5918	GCGUUUUGGAGCAAAUCUG
1166	GAUUUGCUCCAAACGCAG	5920	CUGCGUUUUGGAGCAAAUC
1173	UCCAAACGCAGGCGCCGG	5927	CCGGCGCCUGCGUUUUGGA
1409	UGGAGCGCUGUUGUAAUC	6163	GAUUCACAACAGCGCUCCA
1443	CCUCGCGCAGGCCUCGAC	6197	GUCGAGGCCUCGCCGGAGG
1444	CUCCGGCGAGGCCUCGACU	6198	AGUCGAGGCCUCGCCGGAG
1445	UCCGGCGAGGCCUCGACUU	6199	AAGUCGAGGCCUCGCCGGA
1447	CGGCAGAGGCCUCGACUUCU	6201	AGAAGUCGAGGCCUCGCCG
1857	GACCUGUGGGCGUUGCUA	6611	UAGGCAACGCCACAGGUC
2143	AGACCAGUGCCCCGAAAG	6897	CUUCCGGGGCACUGGUCU
2154	CCGGAAAGACUUUGUAGAG	6908	CUCUACAAAGUCUUUCCGG
2226	CGUCAGCCUCACCGUGACU	6980	AGUCACGGUGAGGCUGACG
2228	UCAGCCUCACCGUGACUAA	6982	UUAGUCACGGUGAGGCUGA
2230	AGCCUCACCGUGACUAACA	6984	UGUUAGUCACGGUGAGGCU
2233	CUCACCGUGACUAACAUGC	6987	GCAUGUAGUCACGGUGAG
2234	UCACCGUGACUAACAUGCC	6988	GGCAUGUUAGUCACGGUGA
2242	ACUAACAUGCCACCGGGCA	6996	UGCCCGGUGGCAUGUUAGU
2244	UAACAUGCCACCGGGCAAG	6998	CUUGCCCGGUGGCAUGUUA
2245	AACAUGCCACCGGGCAAGC	6999	GCUUGCCCGGUGGCAUGUU
2257	GGCAAGCACUCCGGGUAG	7011	CUACCCGGAAGUCUUGCC
2258	GCAAGCACUCCGGGUAGA	7012	UCUACCCGGAAGUGCUUGC
2263	CACUCCGGGUAGACGGCA	7017	UGCCGUCUACCCGGAAGUG
2264	ACUCCGGGUAGACGGCAC	7018	GUGCCGUCUACCCGGAAGU
2267	UCCGGGUAGACGGCACCUC	7021	GAGGUGCCGUCUACCCGGA
2418	GGUCAAUUGGGACUGAGUGU	7172	ACACUCAGUCCAUUGACC
2445	ACGGGUCAGUGAGGGGCAG	7199	CUGCCCCUCACUGACCCGU
2572	CCUGUCGUGCUAAGCAUCA	7326	UGAUGCUUAGCACGACAGG
2644	ACUUCAGCAUGGCACUAG	7398	CUAAGUGCCAUGCUGAAGU
2648	CAGCAUGGCACUAGUGCU	7402	AGCACUAAGUGCCAUGCUG
2655	GCACUAGUGCGUCAUUC	7409	GAAUGACAGCACUAAGUGC
2661	AGUGCGUCAUUCACAGAC	7415	GUCAUGGAAUGACAGCACU
2668	UCAUUCACAGCGGGCUUA	7422	UAAGCCCGUCAUGGAAUGA
2669	CAUUCACAGCGGGCUUAG	7423	CUAAGCCCGUCAUGGAAUG
2676	UGACGGGCUUAGGGCAGUG	7430	CACUGCCCUAAGCCCGUCA
3186	UGCACUGGUCUUCAGCUAC	7940	GUAGCUGAAGACCAGUGCA
3191	UGGUCUUCAGCUACUGGUG	7945	CACCAGUAGCUGAAGACCA
3279	CACACCCUGCCUAUUCUG	8033	CAGAAUAGGCAGGGGUGUG
3297	GUACUCGGGCUCUGACUAC	8051	GUAGUCAGAGCCCAGUAC
3298	UACUCGGGCUCUGACUACA	8052	UGUAGUCAGAGCCCAGUA
3299	ACUCGGGCUCUGACUACAG	8053	CUGUAGUCAGAGCCCAGU
3537	CCACUUUGGAGUUGUCUAC	8291	GUAGACAAUCCAAAGUGG
3538	CACUUUGGAGUUGUCUACC	8292	GGUAGACAAUCCAAAGUG
3560	GAGAAUACAUAGACCAGGC	8314	GCCUGGUCUAUGUAUUCUC
3570	AGACCAGGCCCAGAAUCGA	8324	UCGAUUCUGGGCCUGGUCU
3576	GGCCAGAAUCGAAUCCAA	8330	UUGGAUUCGAUUCUGGGCC

3580	CAGAAUCGAAUCCAAUGUG	8334	CACAUUGGAUUCGAUUCUG
3581	AGAAUCGAAUCCAAUGUGC	8335	GCACAUUGGAUUCGAUUCU
3583	AAUCGAAUCCAAUGUGCCA	8337	UGGCACAUUGGAUUCGAUU
3584	AUCGAAUCCAAUGUGCCAU	8338	AUGGCACAUUGGAUUCGAU
3586	CGAAUCCAAUGUGCCAUCA	8340	UGAUGGCACAUUGGAUUCG
3588	AAUCCAAUGUGCCAUCAAG	8342	CUUGAUGGCACAUUGGAUU
3597	UGCCAAUCAGUCACUAAGU	8351	ACUUAGUGACUUGAUGGCA
3600	CAUCAAGUCACUAAGUCGC	8354	GCGACUUGAGACUUGAUG
3659	GGCUGCUCAUGCGUGGCCU	8413	AGGCCACGCAUGAGCAGCC
3663	GCUCAUGCGUGGCCUGAAC	8417	GUUCAGGCCACGCAUGAGC
3673	GGCCUGAACCCACCCGAAUG	8427	CAUUCGGGUGGUUCAGGCC
3676	CUGAACCCCGAAUGUGC	8430	GCACAUUCGGGUGGUUCAG
3685	CCGAAUGUGCUGGCUCUCA	8439	UGAGAGCCAGCACAUCGCG
3701	UCAUUGGUAUCAUGUUGCC	8455	GGCAACAUGAUACCAUGA
3705	UGGUAUCAUGUUGCCACCU	8459	AGGUGGCAACAUGAUACCA
3748	CCCUAUAUGGCCACGGUG	8502	CACCGUGGCACAUUAGGG
3749	CCUAUAUGUGCCACGGUGA	8503	UCACCGUGGCACAUUAGG
3750	CUAUAUGUGGCCACGGUGAC	8504	GUCACCGUGGCACAUUAG
3752	AUAUGUGGCCACGGUGACCU	8506	AGGUCACCGUGGCACAUU
3773	UCCAGUUAUCCGCUCACC	8527	GGUGAGCGGAUGAACUGGA
3777	GUUCAUCCGCUCACCUCAG	8531	CUGAGGUGAGCGGAUGAAC
3794	AGCGGAACCCACCGUGAA	8548	UUCACGGUGGGGUUCCGCU
3795	GCGGAACCCACCGUGAAG	8549	CUUCACGGUGGGGUUCCGC
3799	AACCCACCGUGAAGGACC	8553	GGUCCUUCACGGUGGGGUU
3871	AAGUUUGUGCACAGGGACC	8625	GGUCCUGUGCACAAACUU

[00213] The siRNAs in subset D have the following characteristics:

- Cross-reactivity: With 19mer in human *MST1R* mRNA, with 17mer/19mer in NHP *MST1R*
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS+SS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤ 20 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF $\geq 1\%$ (pos. 2-18)

[00214] The siRNA sequences in subset D were further selected for more stringent specificity to yield subset E. Subset E includes 112 siRNAs whose base sequences are shown in **Table 7**.

Table 7. Sequences in siRNA subset E

SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
471	UGUGUUUGUAGCCAUACGC	5225	GCGUAUGGCUACAAACACA
472	GUGUUUGUAGCCAUACGCA	5226	UGCGUAUGGCUACAAACAC
474	GUUUGUAGCCAUACGCAAU	5228	AUUGCGUAUGGCUACAAAC
476	UUGUAGCCAUACGCAUUCG	5230	CGAUUGCGUAUGGCUACAA
477	UGUAGCCAUACGCAUUCGC	5231	GCGAUUGCGUAUGGCUACA
480	AGCCAUACGCAUUCGCCUG	5234	CAGGCGAUUGCGUAUGGCU
482	CCAUACGCAUUCGCCUGCA	5236	UGCAGGCGAUUGCGUAUGG
692	GCUUCCUGCAUGACCUAGA	5446	UCUAGGUCAUGCAGGAAGC
717	AGGGACAGCCGUGCAUCUG	5471	CAGAUGCACGGCUGUCCCU
726	CGUGCAUCUGGCAGCGCCA	5480	UGGCGCUGCCAGAUGCACG
753	CUUCUCAGCCCACCAUAAAC	5507	GUUAUGGUGGGCUGAGAAG
763	CACCAUAACCGGCCCGAUG	5517	CAUCGGGCCCGGUUAUGGUG
764	ACCAUAACCGGCCCGAUGA	5518	UCAUCGGGCCCGGUUAUGGU
765	CCAUAACCGGCCCGAUGAC	5519	GUCAUCGGGCCCGGUUAUGG
766	CAUAACCGGCCCGAUGACU	5520	AGUCAUCGGGCCCGGUUAUG

767	AUAACCGGCCCGAUGACUG	5521	CAGUCAUCGGGCCGGUUAU
775	CCCGAUGACUGCCCCGACU	5529	AGUCGGGGCAGUCAUCGGG
776	CCGAUGACUGCCCCGACUG	5530	CAGUCGGGGCAGUCAUCGG
777	CGAUGACUGCCCCGACUGU	5531	ACAGUCGGGGCAGUCAUCG
801	CAGCCCAUUGGGCACCUGU	5555	ACGGGUGCCCAAUUGGGCUG
845	CCUCCUAUUUCUACGUGGC	5599	GCCACGUAGAAAUAAGGAGG
898	AGCCCAAGCUCAGUGUCUA	5652	UAGACACUGAGCGUGGGCU
900	CCCACGCUCAGUGUCUAUC	5654	GAUAGACACUGAGCGUGGG
901	CCACGCUCAGUGUCUAUCA	5655	UGAUAGACACUGAGCGUGG
903	ACGCUCAGUGUCUAUCAGG	5657	CCUGAUAGACACUGAGCGU
910	GUGUCUAUCAGGCGUCUCA	5664	UGAGACGCCUGAUAGACAC
912	GUCUAUCAGGCGUCUCAAG	5666	CUUGAGACGCCUGAUAGAC
913	UCUAUCAGGCGUCUCAAGG	5667	CCUUGAGACGCCUGAUAGA
966	GUUGUCAGUGCUGCCCAAG	5720	CUUGGGCAGCACUGACAAC
976	CUGCCCAAGCAUCUUGUCU	5730	AGACAAGAUGCUGGGGCGAG
977	UGCCCAAGCAUCUUGUCUC	5731	GAGACAAGAUGCUGGGGCA
1001	GUAAUGAAUACGUGCACAG	5755	CUGUGCACGUAAUCAAUAC
1003	AUUGAAUACGUGCACAGCU	5757	AGCUGUGCACGUAAUCAAU
1046	UCCUGACUGUACAGCCGGC	5800	GCCGGCUGUACAGUCAGGA
1049	UGACUGUACAGCCGGCCAG	5803	CUGGCCGGCUGUACAGUCA
1053	UGUACAGCCGGCCAGCGUG	5807	CACGCUGGCCGGCUGUACA
1054	GUACAGCCGGCCAGCGUGA	5808	UCACGCUGGCCGGCUGUAC
1131	GUUGGGUGACUAUCGGGAG	5885	CUCCCGAUAGUCACCCAAC
1134	GGGUGACUAUCGGGAGCUG	5888	CAGCUCCCGAUAGUCACCC
1138	GACUAUCGGGAGCUGGUCC	5892	GGACCAGCUCCCGAUAGUC
1147	GAGCUGGUCCUCGACUGCA	5901	UGCAGUCGAGGACCAGCUC
1153	GUCCUCGACUGCAGAUUUG	5907	CAAAUCUGCAGUCGAGGAC
1155	CCUCGACUGCAGAUUUGCU	5909	AGCAAAUCUGCAGUCGAGG
1157	UCGACUGCAGAUUUGCUCC	5911	GGAGCAAAUCUGCAGUCGA
1162	UGCAGAUUUGCUCCAAAAC	5916	GUUUUGGAGCAAAUCUGCA
1164	CAGAUUUGCUCCAAAACGC	5918	GCGUUUUGGAGCAAAUCUG
1166	GAUUUGCUCCAAAACGCAG	5920	CUGCGUUUUGGAGCAAAUC
1173	UCCAAAACGCAGGCGCCGG	5927	CCGGCGCCUGCGUUUUGGA
1409	UGGAGCGCUGUUGUGAAUC	6163	GAUUCACAACAGCGCUCCA
1443	CCUCCGGCGAGGCCUCGAC	6197	GU CGAGGCCUCGCCGGAGG
1444	CUCCGGCGAGGCCUCGACU	6198	AGUCGAGGCCUCGCCGGAG
1445	UCCGGCGAGGCCUCGACUU	6199	AAGUCGAGGCCUCGCCGGA
1447	CGGCGAGGCCUCGACUUCU	6201	AGAAGUCGAGGCCUCGCCG
1857	GACCUGUGGGCGUUGCCUA	6611	UAGGCAACGCCACAGGUC
2143	AGACCAGUGCCCCGGAAAG	6897	CUUUCCGGGGCAGUGGUCU
2154	CCGGAAAGACUUUGUAGAG	6908	CUCUACAAAGUCUUUCCGG
2226	CGUCAGCCUCACCGUGACU	6980	AGUCACGGUGAGGCUGACG
2228	UCAGCCUCACCGUGACUAA	6982	UUAGUCACGGUGAGGCUGA
2230	AGCCUCACCGUGACUAACA	6984	UGUUAGUCACGGUGAGGCU
2233	CUCACCGUGACUAACAUGC	6987	GCAUGUUAGUCACGUGAGG
2234	UCACCGUGACUAACAUGCC	6988	GGCAUGUUAGUCACGGUGA
2242	ACUAACAUGCCACCGGGCA	6996	UGCCCGGUGGCAUGUUAGU
2244	UAACAUGCCACCGGGCAAG	6998	CUUGCCCGGUGGCAUGUUA
2245	AACAUGCCACCGGGCAAGC	6999	GCUUGCCCGGUGGCAUGUU
2257	GGCAAGCACUUCGGGUAG	7011	CUACCCGGAAGUGCUUGCC
2258	GCAAGCACUUCGGGUAGA	7012	UCUACCCGGAAGUGCUUGC
2263	CACUUCGGGUAGACGGCA	7017	UGCCGUCUACCCGGAAGUG
2264	ACUUCGGGUAGACGGCAC	7018	GUGCCGUCUACCCGGAAGU
2267	UCCGGGUAGACGGCACUC	7021	GAGGUGCCGUCUACCCGGA
2418	GGUCAAUUGGGACUGAGUGU	7172	ACACUCAGUCCAUUGACC
2445	ACGGGUCAGUGAGGGGCGAG	7199	CUGCCCCUCACUGACCCGU
2572	CCUGUCGUGCUAAGCAUCA	7326	UGAUGCUUAGCACGCACAGG
2644	ACUUCAGCAUGGCACUUAAG	7398	CUAAGUGCCAUGCUGAAAGU
2648	CAGCAUGGCACUUAAGUCU	7402	AGCACUAAGUGCCAUGCUG
2655	GCACUUAGUGCUGUCAUUC	7409	GAAUGACAGCACUAAGUGC
2661	AGUGCUGUCAUCCAUGAC	7415	GUCAUGGAAUGACAGCACU

2668	UCAUCCAUGACGGGCUUA	7422	UAAGCCCUGCAUGGAAUGA
2669	CAUCCAUGACGGGCUUAG	7423	CUAAGCCCUGCAUGGAAUG
2676	UGACGGGCUUAGGGCAGUG	7430	CACUGCCCUAAGCCCUGCA
3186	UGCACUGGUCUUCAGCUAC	7940	GUAGCUGAAGACCAGUGCA
3191	UGGUCUUCAGCUACUGGUG	7945	CACCAGUAGCUGAAGACCA
3279	CACACCCUGCCUAUUCUG	8033	CAGAAUAGGCAGGGGUGUG
3297	GUACUCGGGCUCUGACUAC	8051	GUAGUCAGAGCCCAGUAC
3298	UACUCGGGCUCUGACUACA	8052	UGUAGUCAGAGCCCAGUA
3299	ACUCGGGCUCUGACUACAG	8053	CUGUAGUCAGAGCCCAGU
3560	GAGAAUACAUAAGACCAGGC	8314	GCCUGGUCUAUGUAUUCUC
3570	AGACCAGGCCCAGAAUCGA	8324	UCGAUUCUGGGCCUGGUCU
3576	GGCCAGAAUCGAAUCCAA	8330	UUUGAUUCGAUUCUGGGCC
3580	CAGAAUCGAAUCCAUGUG	8334	CACAUUGGAUUCGAUUCUG
3581	AGAAUCGAAUCCAUGUGC	8335	GCACAUUGGAUUCGAUUCU
3583	AAUCGAAUCCAUGUGCCA	8337	UGGCACAUUGGAUUCGAUU
3584	AUCGAAUCCAUGUGCCAU	8338	AUGGCACAUUGGAUUCGAU
3586	CGAAUCCAUGUGCCAUCA	8340	UGAUGGCACAUUGGAUUCG
3588	AAUCCAUGUGCCAUCAAG	8342	CUUGAUGGCACAUUGGAUU
3597	UGCCAUCAAGUCACUAAGU	8351	ACUUAUGAGACUUGAUGGCA
3600	CAUCAAGUCACUAAGUCGC	8354	GCGACUUAUGAGACUUGAUG
3659	GGCUGCUCUAGCGUGGCCU	8413	AGGCCACGCAUGAGCAGCC
3673	GGCCUGAACCACCCGAAUG	8427	CAUUCGGGUGGUUCAGGCC
3676	CUGAACCACCCGAAUGUGC	8430	GCACAUUCGGGUGGUUCAG
3685	CCGAAUGUGCUGGCUCUCA	8439	UGAGAGCCAGCACAUCGG
3701	UCAUUGGUAUCAUGUUGCC	8455	GGCAACAUGAUACCAAUGA
3705	UGGUAUCAUGUUGCCACCU	8459	AGGUGGCAACAUGAUACCA
3748	CCCUAUAUGUGCCACGGUG	8502	CACCGUGGCACAUAUAGGG
3749	CCUAUAUGUGCCACGGUGA	8503	UCACCGUGGCACAUAUAGG
3750	CUAUAUGUGCCACGGUGAC	8504	GUACCGUGGCACAUAUAG
3752	AUAUGUGCCACGGUGACCU	8506	AGGUCACCGUGGCACAUAU
3773	UCCAGUUCAUCCGCUCACC	8527	GGUGAGCGGAUGAACUGGA
3777	GUUCAUCCGCUCACCUCAG	8531	CUGAGGUGAGCGGAUGAAC
3794	AGCGGAACCCACCGUGAA	8548	UUCACGGUGGGGUUCCGCU
3795	GCGGAACCCACCGUGAAG	8549	CUUCACGGUGGGGUUCCGC
3799	AACCCACCGUGAAGGACC	8553	GGUCCUUCACGGUGGGGUU
3871	AAGUUUGUGCACAGGGACC	8625	GGUCCUUGUGCACAAACUU

[00215] The siRNAs in subset E have the following characteristics:

- Cross-reactivity: With 19mer in human *MST1R* mRNA, with 17mer/19mer in NHP *MST1R*
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS+SS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤15 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[00216] Subset F includes 103 siRNAs. The siRNAs in subset F include siRNAs from subset A, and are included in **Table 8**. In some cases, the sense strand of any of the siRNAs of subset F comprises modification pattern 6S (**Table 9**). In some cases, the antisense strand of any of the siRNAs of subset F comprises modification pattern 7AS (**Table 9**). In some cases, the sense strand of any of the siRNAs of subset F contains an alternative modification pattern (**Table 10**). In some cases, the antisense strand of any of the siRNAs of subset F comprises modification pattern 7AS (**Table 10**). The siRNAs in subset F may comprise any other modification pattern(s). In **Table 9** and **Table 10**, Nf (e.g. Af, Cf, Gf, Tf, or Uf)

is a 2' fluoro-modified nucleoside, n (e.g. a, c, g, t, or u) is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

Table 8. Sequences in siRNA subset F

SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
469	GCUGUGUUUGUAGCCAUAC	5223	GUAUGGCUACAAAACACAGC
471	UGUGUUUGUAGCCAUACGC	5225	GCGUAUGGCUACAAAACACA
475	UUUGUAGCCAUACGCAAUC	5229	GAUUGCGUAUGGCUACAAA
476	UUGUAGCCAUACGCAAUCG	5230	CGAUUGCGUAUGGCUACAA
477	UGUAGCCAUACGCAAUCGC	5231	GCGAUUGCGUAUGGCUACA
483	CAUACGCAAUCGCCUGCAU	5237	AUGCAGGCGAUUGCGUAUG
692	GCUUCCUGCAUGACCUAGA	5446	UCUAGGUC AUGCAGGAAGC
693	CUUCCUGCAUGACCUAGAG	5447	CUUAGGUC AUGCAGGAAG
753	CUUCUCAGCCCACCAUAAAC	5507	GUUAUGGUGGGGUGAGAAAG
845	CCUCCUAUUUCUACGUGGC	5599	GCCACGUAGAAAUAAGGAGG
901	CCACGCUCAGUGUCUAUCA	5655	UGAUAGACACUGAGCGUGG
908	CAGUGUCUAUCAGGCGUCU	5662	AGACGCCUGAUAGACACUG
910	GUGUCUAUCAGGCGUCUCA	5664	UGAGACGCCUGAUAGACAC
911	UGUCUAUCAGGCGUCUCA	5665	UUGAGACGCCUGAUAGACA
912	GUCUAUCAGGCGUCUCAAG	5666	CUUGAGACGCCUGAUAGAC
915	UAUCAGGCGUCUCAAGGCU	5669	AGCCUUGAGACGCCUGAUA
977	UGCCCAAGCAUCUUGUCUC	5731	GAGACAAGAUGCUUGGGCA
985	CAUCUUGUCUCCUACAGUA	5739	UACUGUAGGAGACAAGAUG
989	UUGUCUCCUACAGUAUUGA	5743	UCAAUACUGUAGGAGACAA
990	UGUCUCCUACAGUAUUGAA	5744	UUCAAUACUGUAGGAGACA
992	UCUCCUACAGUAUUGAAUA	5746	UAUUCAAUACUGUAGGAGA
1001	GUAAUUGAAUACGUCACAG	5755	CUGUGCACGUAUUCAAUAC
1003	AUUGAAUACGUCACAGCU	5757	AGCUGGCACGUAUUCAAU
1004	UUGAAUACGUCACAGCUU	5758	AAGCUGGCACGUAUUCAA
1006	GAAUACGUCACAGCUUCC	5760	GGAAGCUGGCACGUAUUC
1043	ACUUCUGACUGUACAGCC	5797	GGCUGUACAGUCAGGAAGU
1124	AGCCAGAGUUGGGUGACUA	5878	UAGUCACCCAACUCUGGCU
1152	GGUCCUGCAGUCAGAUUU	5906	AAAUCUGCAGUCGAGGACC
1153	GUCCUGCAGUCAGAUUUG	5907	CAAAUCUGCAGUCGAGGAC
1154	UCCUGCAGUCAGAUUUGC	5908	GCAAAUCUGCAGUCGAGGA
1155	CCUCGACUCAGAUUUGCU	5909	AGCAAAUCUGCAGUCGAGG
1158	CGACUGCAGAUUUGCUCCA	5912	UGGAGCAAAUCUGCAGUCG
1161	CUGCAGAUUUGCUCAAAA	5915	UUUUGGAGCAAAUCUGCAG
1162	UGCAGAUUUGCUCAAAAAC	5916	GUUUUGGAGCAAAUCUGCA
1164	CAGAUUUGCUCAAAAACGC	5918	GCGUUUUGGAGCAAAUCUG
1408	GUGGAGCGCUGUUGUGAAU	6162	AUUCACAACAGCGCUCCAC
1409	UGGAGCGCUGUUGUGAAUC	6163	GAUUCACAACAGCGCUCCA
2124	CAAGGACAGCUCAAAACUC	6878	GAGUUUUGAGCUGUCCUUG
2150	UGCCCCGAAAGACUUUGU	6904	ACAAAGUCUUUCCGGGGCA
2151	GCCCCGAAAGACUUUGUA	6905	UACAAAGUCUUUCCGGGGC
2152	CCCCGAAAGACUUUGUAG	6906	CUACAAAGUCUUUCCGGGG
2153	CCCGGAAAGACUUUGUAGA	6907	UCUACAAAGUCUUUCCGGG
2165	UUGUAGAGGAGUUUGAGUG	6919	CACUCAAACUCCUCUACAA
2230	AGCCUCACCGUGACUAACA	6984	UGUUAGUCACGGUGAGGCU
2233	CUCACCGUGACUAACAUGC	6987	GCAUGUUAGUCACGGUGAG
2234	UCACCGUGACUAACAUGCC	6988	GGCAUGUUAGUCACGGUGA
2235	CACCGUGACUAACAUGCCA	6989	UGGCAUGUUAGUCACGGUG
2318	UGCUGAUAGCAGUGCAACC	7072	GGUUGCAGUCUAUACGCA
2366	GUCUCACUCUUGAAGGCCA	7120	UGGCCUUAAGAGUGAGAC
2369	UCACUCUUGAAGGCCAGAG	7123	CUCUGGCCUUAAGAGUGA
2412	UGUGCUGGUCAAUGGGACU	7166	AGUCCAUUGACCAGCACA
2418	GGUCA AUGGGACUGAGUGU	7172	ACACUCAGUCCAUUGACC
2420	UCA AUGGGACUGAGUGUCU	7174	AGACACUCAGUCCAUUGA
2421	CAAUGGGACUGAGUGUCUG	7175	CAGACACUCAGUCCAUUG

2427	GACUGAGUGUCUGCUAGCA	7181	UGCUAGCAGACACUCAGUC
2455	GAGGGGCAGCUUUU AUGUG	7209	CACAUAAAAGCUGCCCUC
2460	GCAGCUUUU AUGUGCCACA	7214	UGUGGCACAUAAAAGCUGC
2462	AGCUUUU AUGUGCCACACC	7216	GGUGUGGCACAUAAAAGCU
2566	GAAGACCCUGUCGUGCUAA	7320	UUAGCACGACAGGGUCUUC
2567	AAGACCCUGUCGUGCUAAG	7321	CUUAGCACGACAGGGUCUU
2581	CUAAGCAUCAGCCCCAACU	7335	AGUUUGGGCUGAUGCUUAG
2582	UAAGCAUCAGCCCCAACUG	7336	CAGUUUGGGCUGAUGCUUA
2628	CUGUGGCCAGCAUCUAACU	7382	AGUUAGAUGCUGGCCACAG
2644	ACUUCAGCAUGGCACUAG	7398	CUAAGUGCCAUUGCUGAAGU
2646	UUCAGCAUGGCACUAGUG	7400	CACUAAGUGCCAUUGCUGAA
2648	CAGCAUGGCACUAGUGCU	7402	AGCACUAAGUGCCAUUGCUG
2656	CACUUAUGUCUGUCAUCC	7410	GGAAUGACAGCACUAAGUG
2663	UGCUGUCAUCCAUGACGG	7417	CCGUCAUGGAAUGACAGCA
2666	UGUCAUCCAUGACGGGCU	7420	AGCCCGUCAUGGAAUGACA
2669	CAUCCAUGACGGGCUUAG	7423	CUAAGCCCGUCAUGGAAUG
2670	AUCCAUGACGGGCUUAGG	7424	CCUAAGCCCGUCAUGGAAU
2889	UGAGGAGCAUGCCAUAAG	7643	CUUAAUGGCAUGCUCUACA
2895	GCAUGCCAUAAGUUUGAG	7649	CUCAAACUUAAGGCAUGC
3084	UAUCCUGGGUAGAGUGGUG	7838	CACCACUCUACCCAGGAUA
3191	UGGUCUUCAGCUACUGGUG	7945	CACCAGUAGCUGAAGACCA
3223	CUAGUUCUCCUCCCAACC	7977	GGUUGGGAGGAAGAACUAG
3298	UACUCGGGCUCUGACUACA	8052	UGUAGUCAGAGCCCAGUA
3538	CACUUUGGAGUUGUCUACC	8292	GGUAGACAACUCCAAAGUG
3560	GAGAAUACAUAGACCAGGC	8314	GCCUGGUCUAUGUAUUCUC
3568	AUAGACCAGGCCAGAAUC	8322	GAUUCUGGGCCUGGUCUAU
3576	GGCCCAGAAUCGAAUCCAA	8330	UUGGAUUCGAUUCUGGGCC
3578	CCCAGAAUCGAAUCCAAUG	8332	CAUUGGAUUCGAUUCUGGG
3580	CAGAAUCGAAUCCAAUGUG	8334	CACAUUGGAUUCGAUUCUG
3581	AGAAUCGAAUCCAAUGUGC	8335	GCACAUUGGAUUCGAUUCU
3582	GAAUCGAAUCCAAUGUGCC	8336	GGCACAUUGGAUUCGAUUC
3586	CGAAUCCAAUGUGCCAUCA	8340	UGAUGGCACAUUGGAUUCG
3587	GAAUCCAAUGUGCCAUCAA	8341	UUGAUGGCACAUUGGAUUC
3592	CAAUGUGCCAUCAGUCAC	8346	GUGACUUGAUGGCACAUUG
3595	UGUGCCAUCAGUCACUAA	8349	UUAGUGACUUGAUGGCACA
3596	GUGCCAUCAGUCACUAAG	8350	CUUAGUGACUUGAUGGCAC
3597	UGCCAUCAGUCACUAAGU	8351	ACUUGAGACUUGAUGGCA
3600	CAUCAAGUCACUAAGUCGC	8354	GCGACUUGAGACUUGAUG
3701	UCAUUGGUUAUGUUGCC	8455	GGCAACAUGAUACCAAUGA
3749	CCUAUAUGUGCCACGGUGA	8503	UCACCGUGGCACAUUAGG
3750	CUAUAUGUGCCACGGUGAC	8504	GUCACCGUGGCACAUUAG
3751	UAUAUGUGCCACGGUGACC	8505	GGUCACCGUGGCACAUUA
3752	AUAUGUGCCACGGUGACCU	8506	AGGUCACCGUGGCACAUUA
3871	AAGUUUGUGCACAGGGACC	8625	GGUCCUGUGCACAAACUU
4284	GGUGGAGCAGAUAGUGUCU	9038	AGACACUAUCUGCUCCACC
4292	AGAUAGUGUCUGCACUGCU	9046	AGCAGUGCAGACACUAUCU
4311	UGGGGACCAUUAUGUGCAG	9065	CUGCACAUAAUGGUCCCA
4313	GGGACCAUUAUGUGCAGCU	9067	AGCUGCACAUAAUGGUCCC
4333	CCAGCAACCUACAUGAACU	9087	AGUUCAUGUAGGUUGCUGG

Table 9. Modified siRNA subset F sequences (a.k.a. subset G)

siRNA Name	SEQ ID NO:	Sense strand sequence (5'-3')	SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 9509	9509	GfscsUfgUfgUfuUfgUfaGfcCfaUfaAfsusu	9612	usUfsaUfgGfcUfaCfaAfaCfaCfaGfcsusu
siRNA 9510	9510	UfsgsUfgUfuUfgUfaGfcCfaUfaCfGfAfsusu	9613	usCfsgUfaUfgGfcUfaCfaAfaCfaCfasusu
siRNA 9511	9511	UfsusUfgUfaGfcCfaUfaCfGfCfaAfuAfsusu	9614	usAfsuUfgCfGfUfaUfgGfcUfaCfaAfasusu
siRNA 9512	9512	UfsusGfuAfgCfcAfuAfcGfcAfaUfcAfsusu	9615	usGfsaUfuGfcGfuAfuGfgCfuAfcAfasusu

siRNA 9513	9513	UfsgsUfaGfcCfaUfaCfGcCfaAfuCfGfAfsusu	9616	usCfsgAfuUfgCfGfUfaUfgGfcUfaCfasusu
siRNA 9514	9514	CfsasUfaCfGcCfaAfuCfGcCfcUfgCfaAfsusu	9617	usUfsgCfaGfgCfGfAfuUfgCfGfUfaUfgsusu
siRNA 9515	9515	GfscsUfuCfcUfgCfaUfgAfcCfuAfgAfsusu	9618	usCfsuAfgGfuCfaUfgCfaGfgAfaGfcsusu
siRNA 9516	9516	CfsusUfcCfuGfcAfuGfaCfcUfaGfaAfsusu	9619	usUfscUfaGfgUfcAfuGfcAfgGfaAfgsusu
siRNA 9517	9517	CfsusUfcUfaCfGcCfcCfaCfcAfuAfaAfsusu	9620	usUfsuAfuGfgUfgGfgCfuGfaGfaAfgsusu
siRNA 9518	9518	CfscsUfcCfuAfuUfuCfuAfcGfuGfgAfsusu	9621	usCfscAfcGfuAfgAfaAfuAfgGfaGfgsusu
siRNA 9519	9519	CfscsAfcGfcUfcAfgUfgUfcUfaUfcAfsusu	9622	usGfsaUfaGfaCfaCfuGfaGfcGfuGfgsusu
siRNA 9520	9520	CfsasGfuGfuCfuAfuCfaGfgCfGfUfcAfsusu	9623	usGfsaCfGcCfcUfgAfuAfgAfcAfcUfgsusu
siRNA 9521	9521	GfsusGfuCfuAfuCfaGfgCfGfUfcUfcAfsusu	9624	usGfsaGfaCfGcCfcUfgAfuAfgAfcAfcfsusu
siRNA 9522	9522	UfsgsUfcUfaUfaCfGfGfcCfuCfuCfaAfsusu	9625	usUfsgAfgAfcGfcCfuGfaUfaGfaCfasusu
siRNA 9523	9523	GfsusCfuAfuCfaGfgCfGfUfcUfcAfaAfsusu	9626	usUfsuGfaGfaCfGcCfcUfgAfuAfgAfcfsusu
siRNA 9524	9524	UfsasUfcAfgGfcGfuCfuCfaAfgGfcAfsusu	9627	usGfscCfuUfgAfgAfcGfcCfuGfaUfasusu
siRNA 9525	9525	UfsgsCfcCfaAfgCfaUfcUfuGfuCfuAfsusu	9628	usAfsGfcAfaGfaUfgCfuUfgGfgCfasusu
siRNA 9526	9526	CfsasUfcUfuGfuCfuCfcUfaCfaGfuAfsusu	9629	usAfsCufgUfaGfgAfgAfcAfaGfaUfgsusu
siRNA 9527	9527	UfsusGfuCfuCfcUfaCfaGfuAfuUfgAfsusu	9630	usCfsaAfuAfcUfgUfaGfgAfgAfcAfasusu
siRNA 9528	9528	UfsgsUfcUfcCfuAfcAfgUfaUfuGfaAfsusu	9631	usUfscAfaUfaCfuGfuAfgGfaGfaCfasusu
siRNA 9529	9529	UfscsUfcCfuAfcAfgUfaUfuGfaAfuAfsusu	9632	usAfsuUfcAfaUfaCfuGfuAfgGfaGfasusu
siRNA 9530	9530	GfsusAfuUfgAfaUfaCfGfUfgCfaCfaAfsusu	9633	usUfsgUfgCfaCfGfUfaUfuCfaAfuAfcfsusu
siRNA 9531	9531	AfsusUfgAfaUfaCfGfUfgCfaCfaGfcAfsusu	9634	usGfscUfgUfgCfaCfGfUfaUfuCfaAfususu
siRNA 9532	9532	UfsusGfaAfuAfcGfuGfcAfcAfgCfuAfsusu	9635	usAfsGcfuGfuGfcAfcGfuAfuUfcAfasusu
siRNA 9533	9533	GfsasAfuAfcGfuGfcAfcAfgCfuUfcAfsusu	9636	usGfsaAfgCfuGfuGfcAfcGfuAfuUfcfsusu
siRNA 9534	9534	AfscsUfuCfcUfgAfcUfgUfaCfaGfcAfsusu	9637	usGfscUfgUfaCfaGfuCfaGfgAfaGfususu
siRNA 9535	9535	AfsgsCfcAfgAfgUfuGfgGfuGfaCfuAfsusu	9638	usAfsGufcAfcCfcAfaCfuCfuGfgCfususu
siRNA 9536	9536	GfsgsUfcCfuCfGfAfcUfgCfaGfaUfuAfsusu	9639	usAfsaUfcUfgCfaGfuCfGfAfgGfaCfcfsusu
siRNA 9537	9537	GfsusCfcUfcGfaCfuGfcAfgAfuUfuAfsusu	9640	usAfsaAfuCfuGfcAfgUfcGfaGfgAfcfsusu
siRNA 9538	9538	UfscsCfuCfGfAfcUfgCfaGfaUfuUfgAfsusu	9641	usCfsaAfaUfcUfgCfaGfuCfGfAfgGfasusu
siRNA 9539	9539	CfscsUfcGfaCfuGfcAfgAfuUfuGfcAfsusu	9642	usGfscAfaAfuCfuGfcAfgUfcGfaGfgsusu
siRNA 9540	9540	CfsgsAfcUfgCfaGfaUfuUfgCfuCfcAfsusu	9643	usGfsgAfgCfaAfaUfcUfgCfaGfuCfGfsusu
siRNA 9541	9541	CfsusGfcAfgAfuUfuGfcUfcCfaAfaAfsusu	9644	usUfsuUfgGfaGfcAfaAfuCfuGfcAfgsusu
siRNA 9542	9542	UfsgsCfaGfaUfuUfgCfuCfcAfaAfaAfsusu	9645	usUfsuUfuGfgAfgCfaAfaUfcUfgCfasusu
siRNA 9543	9543	CfsasGfaUfuUfgCfuCfcAfaAfaCfGfAfsusu	9646	usCfsgUfuUfuGfgAfgCfaAfaUfcUfgsusu
siRNA 9544	9544	GfsusGfgAfgCfGfCfuGfuUfgUfgAfaAfsusu	9647	usUfsuCfaCfaAfcAfgCfGfCfuCfcAfcfsusu
siRNA 9545	9545	UfsgsGfaGfcGfcUfgUfuGfuGfaAfuAfsusu	9648	usAfsuUfcAfcAfaCfaGfcGfcUfcCfasusu
siRNA 9546	9546	CfsasAfgGfaCfaGfcUfcAfaAfaCfuAfsusu	9649	usAfsGufuUfuGfaGfcUfgUfcCfuUfgsusu

siRNA 9547	9547	UfsgsCfcCfcGfgAfaAfgAfcUfuUfgAfsusu	9650	usCfsaAfaGfuCfuUfuCfcGfgGfgCfasusu
siRNA 9548	9548	GfscsCfcCfgGfaAfaGfaCfuUfuGfuAfsusu	9651	usAfsaAfaAfgUfcUfuUfcCfgGfgGfcsusu
siRNA 9549	9549	CfscsCfcGfgAfaAfgAfcUfuUfgUfaAfsusu	9652	usUfsaCfaAfaGfuCfuUfuCfcGfgGfgsusu
siRNA 9550	9550	CfscsCfgGfaAfaGfaCfuUfuGfuAfgAfsusu	9653	usCfsuAfcAfaAfgUfcUfuUfcCfgGfgsusu
siRNA 9551	9551	UfsusGfuAfgAfgGfaGfuUfuGfaGfuAfsusu	9654	usAfsaUfcAfaAfcUfcCfuCfuAfcAfasusu
siRNA 9552	9552	AfsgsCfcUfcAfcCfcGfgUfgAfcUfaAfcAfsusu	9655	usGfsuUfaGfuCfaCfgGfuGfaGfgCfususu
siRNA 9553	9553	CfsusCfaCfcGfuGfaCfuAfaCfaUfgAfsusu	9656	usCfsaUfgUfuAfgUfcAfcGfgUfgAfgsusu
siRNA 9554	9554	UfscsAfcCfcGfgUfgAfcUfaAfcAfuGfcAfsusu	9657	usGfscAfuGfuUfaGfuCfaCfgGfuGfasusu
siRNA 9555	9555	CfsasCfcGfuGfaCfuAfaCfaUfgCfcAfsusu	9658	usGfsgCfaUfgUfuAfgUfcAfcGfgUfgsusu
siRNA 9556	9556	UfsgsCfuGfaUfaGfcAfgUfgCfaAfcAfsusu	9659	usGfsuUfgCfaCfuGfcUfaUfcAfgCfasusu
siRNA 9557	9557	GfsusCfuCfaCfuCfuUfgAfaGfgCfcAfsusu	9660	usGfsgCfcUfuCfaAfgAfgUfgAfgAfcusu
siRNA 9558	9558	UfscsAfcUfcUfuGfaAfgGfcCfaGfaAfsusu	9661	usUfscUfgGfcCfuUfcAfaGfaGfuGfasusu
siRNA 9559	9559	UfsgsUfgCfuGfgUfcAfaUfgGfgAfcAfsusu	9662	usGfsuCfcCfaUfuGfaCfcAfgCfaCfasusu
siRNA 9560	9560	GfsgsUfcAfaUfgGfgAfcUfgAfgUfgAfsusu	9663	usCfsaCfuCfaGfuCfcCfaUfuGfaCfcsusu
siRNA 9561	9561	UfscsAfaUfgGfgAfcUfgAfgUfgUfcAfsusu	9664	usGfsaCfaCfuCfaGfuCfcCfaUfuGfasusu
siRNA 9562	9562	CfsasAfuGfgGfaCfuGfaGfuGfuCfuAfsusu	9665	usAfsaAfcAfcUfcAfgUfcCfcAfuUfgsusu
siRNA 9563	9563	GfsasCfuGfaGfuGfuCfuGfcUfaGfcAfsusu	9666	usGfscUfaGfcAfgAfcAfcUfcAfgUfcsusu
siRNA 9564	9564	GfsasGfgGfgCfaGfcUfuUfuAfuGfuAfsusu	9667	usAfsaAfuAfaAfaGfcUfgCfcCfcUfcsusu
siRNA 9565	9565	GfscsAfgCfuUfuUfaUfgUfgCfcAfcAfsusu	9668	usGfsuGfgCfaCfaUfaAfaAfgCfuGfcsusu
siRNA 9566	9566	AfsgsCfuUfuUfaUfgUfgCfcAfcAfcAfsusu	9669	usGfsuGfuGfgCfaCfaUfaAfaAfgCfususu
siRNA 9567	9567	GfsasAfgAfcCfcUfgUfcGfuGfcUfaAfsusu	9670	usUfsaGfcAfcGfaCfaGfgGfuCfuUfcsusu
siRNA 9568	9568	AfsasGfaCfcCfuGfuCfgUfgCfuAfaAfsusu	9671	usUfsuAfgCfaCfgAfcAfgGfgUfcUfususu
siRNA 9569	9569	CfsusAfaGfcAfuCfaGfcCfcCfaAfcAfsusu	9672	usGfsuUfgGfgGfcUfgAfuGfcUfuAfgsusu
siRNA 9570	9570	UfsasAfgCfaUfcAfgCfcCfcAfaCfuAfsusu	9673	usAfsaUfuGfgGfgCfuGfaUfgCfuUfasusu
siRNA 9571	9571	CfsusGfuGfgCfcAfgCfaUfcUfaAfcAfsusu	9674	usGfsuUfaGfaUfgCfuGfgCfcAfcAfgsusu
siRNA 9572	9572	AfscsUfuCfaGfcAfuGfgCfaCfuUfaAfsusu	9675	usUfsaAfgUfgCfcAfuGfcUfgAfaGfususu
siRNA 9573	9573	UfsusCfaGfcAfuGfgCfaCfuUfaGfuAfsusu	9676	usAfsaUfaAfgUfgCfcAfuGfcUfgAfasusu
siRNA 9574	9574	CfsasGfcAfuGfgCfaCfuUfaGfuGfcAfsusu	9677	usGfscAfcUfaAfgUfgCfcAfuGfcUfgsusu
siRNA 9575	9575	CfsasCfuUfaGfuGfcUfgUfcAfuUfcAfsusu	9678	usGfsaAfuGfaCfaGfcAfcUfaAfgUfgsusu
siRNA 9576	9576	UfsgsCfuGfuCfaUfuCfcAfuGfaCfgAfsusu	9679	usCfsgUfcAfuGfgAfaUfgAfcAfgCfasusu
siRNA 9577	9577	UfsgsUfcAfuUfcCfaUfgAfcGfgGfcAfsusu	9680	usGfscCfcGfuCfaUfgGfaAfuGfaCfasusu
siRNA 9578	9578	CfsasUfuCfcAfuGfaCfgGfgCfuUfaAfsusu	9681	usUfsaAfgCfcCfgUfcAfuGfgAfaUfgsusu
siRNA 9579	9579	AfsusUfcCfaUfgAfcGfgGfcUfuAfgAfsusu	9682	usCfsuAfaGfcCfcGfuCfaUfgGfaAfususu
siRNA 9580	9580	UfsgsAfgGfaGfcAfuGfcCfaUfuAfaAfsusu	9683	usUfsuAfaUfgGfcAfuGfcUfcCfuCfasusu

siRNA 9581	9581	GfscsAfuGfcCfaUfuAfaGfuUfuGfaAfsusu	9684	usUfscAfaAfcUfuAfaUfgGfcAfuGfcsusu
siRNA 9582	9582	UfsasUfcCfuGfgGfuAfgAfgUfgGfuAfsusu	9685	usAfsccfaCfuCfuAfcCfcAfgGfaUfasusu
siRNA 9583	9583	UfsgsGfuCfuUfcAfgCfuAfcUfgGfuAfsusu	9686	usAfsccfaGfuAfgCfuGfaAfgAfcCfasusu
siRNA 9584	9584	CfsusAfgUfuCfuUfcCfuCfcCfaAfcAfsusu	9687	usGfsuUfgGfgAfgGfaAfgAfaCfuAfgsusu
siRNA 9585	9585	UfsasCfuCfgGfgCfuCfuGfaCfuAfcAfsusu	9688	usGfsuAfgUfcAfgAfgCfcCfgAfgUfasusu
siRNA 9586	9586	CfsasCfuUfuGfgAfgUfuGfuCfuAfcAfsusu	9689	usGfsuAfgAfcAfaCfuCfcAfaAfgUfgsusu
siRNA 9587	9587	GfsasGfaAfuAfcAfuAfgAfcCfaGfgAfsusu	9690	usCfscUfgGfuCfuAfuGfuAfuUfcUfcsusu
siRNA 9588	9588	AfsusAfgAfcCfaGfgCfcCfaGfaAfuAfsusu	9691	usAfsuUfcUfgGfgCfcUfgGfuCfuAfususu
siRNA 9589	9589	GfsgsCfcCfaGfaAfuCfgAfaUfcCfaAfsusu	9692	usUfsgGfaUfuCfgAfuUfcUfgGfgCfcsusu
siRNA 9590	9590	CfscsCfaGfaAfuCfgAfaUfcCfaAfuAfsusu	9693	usAfsuUfgGfaUfuCfgAfuUfcUfgGfgsusu
siRNA 9591	9591	CfsasGfaAfuCfgAfaUfcCfaAfuGfuAfsusu	9694	usAfsccfuUfgGfaUfuCfgAfuUfcUfgsusu
siRNA 9592	9592	AfsgsAfaUfcGfaAfuCfcAfaUfgUfgAfsusu	9695	usCfsaCfaUfuGfgAfuUfcGfaUfuCfususu
siRNA 9593	9593	GfsasAfuCfgAfaUfcCfaAfuGfuGfcAfsusu	9696	usGfscAfcAfuUfgGfaUfuCfgAfuUfcsusu
siRNA 9594	9594	CfsgsAfaUfcCfaAfuGfuGfcCfaUfcAfsusu	9697	usGfsaUfgGfcAfcAfuUfgGfaUfuCfcsusu
siRNA 9595	9595	GfsasAfuCfcAfaUfgUfgCfcAfuCfaAfsusu	9698	usUfsgAfuGfgCfaCfaUfuGfgAfuUfcsusu
siRNA 9596	9596	CfsasAfuGfuGfcCfaUfcAfaGfuCfaAfsusu	9699	usUfsgAfcUfuGfaUfgGfcAfcAfuUfgsusu
siRNA 9597	9597	UfsgsUfgCfcAfuCfaAfgUfcAfcUfaAfsusu	9700	usUfsgAfuGfaCfuUfgAfuGfgCfaCfasusu
siRNA 9598	9598	GfsusGfcCfaUfcAfaGfuCfaCfuAfaAfsusu	9701	usUfsuAfgUfgAfcUfuGfaUfgGfcAfcfsusu
siRNA 9599	9599	UfsgsCfcAfuCfaAfgUfcAfcUfaAfgAfsusu	9702	usCfsuUfaGfuGfaCfuUfgAfuGfgCfasusu
siRNA 9600	9600	CfsasUfcAfaGfuCfaCfuAfaGfuCfgAfsusu	9703	usCfsgAfcUfuAfgUfgAfcUfuGfaUfgsusu
siRNA 9601	9601	UfscsAfuUfgGfuAfuCfaUfgUfuGfcAfsusu	9704	usGfscAfaCfaUfgAfuAfcCfaAfuGfasusu
siRNA 9602	9602	CfscsUfaUfaUfgUfgCfcAfcGfgUfgAfsusu	9705	usCfsaCfcGfuGfgCfaCfaUfaUfaGfgsusu
siRNA 9603	9603	CfsusAfuAfuGfuGfcCfaCfgGfuGfaAfsusu	9706	usUfscAfcCfgUfgGfcAfcAfuAfuAfgsusu
siRNA 9604	9604	UfsasUfaUfgUfgCfcAfcGfgUfgAfcAfsusu	9707	usGfsuCfaCfcGfuGfgCfaCfaUfaUfasusu
siRNA 9605	9605	AfsusAfuGfuGfcCfaCfgGfuGfaCfcAfsusu	9708	usGfsgUfcAfcCfgUfgGfcAfcAfuAfususu
siRNA 9606	9606	AfsasGfuUfuGfuGfcAfcAfgGfgAfcAfsusu	9709	usGfsuCfcCfuGfuGfcAfcAfaAfcUfususu
siRNA 9607	9607	GfsgsUfgGfaGfcAfgAfuAfgUfgUfcAfsusu	9710	usGfsaCfaCfuAfuCfuGfcUfcCfaCfcsusu
siRNA 9608	9608	AfsgsAfuAfgUfgUfcUfgCfaCfuGfcAfsusu	9711	usGfscAfgUfgCfaGfaCfaCfuAfuCfususu
siRNA 9609	9609	UfsgsGfgGfaCfcAfuUfaUfgUfgCfaAfsusu	9712	usUfsgCfaCfaUfaAfuGfgUfcCfcCfasusu
siRNA 9610	9610	GfsgsGfaCfcAfuUfaUfgUfgCfaGfcAfsusu	9713	usGfscUfgCfaCfaUfaAfuGfgUfcCfcsusu
siRNA 9611	9611	CfscsAfgCfaAfcCfuAfcAfuGfaAfcAfsusu	9714	usGfsuUfcAfuGfuAfgGfuUfgCfuGfgsusu

Table 10. Alternatively modified siRNA subset F sequences (a.k.a. subset H)

siRNA Name	SEQ ID NO:	sense strand sequence (5'-3')	SEQ ID NO:	antisense strand sequence (5'-3')
ETD01363	9715	gscsugUfgUfuUfgUfagcc auaasusu	9612	usUfsaUfgGfcUfaCfaAfaCfa CfaGfcsusu
ETD01364	9716	usgsugUfuUfgUfagccaua cgasusu	9613	usCfsgUfaUfgGfcUfaCfaAfa CfaCfasusu
ETD01365	9717	ususugUfagCfCfaUfacgc aauasusu	9614	usAfsuUfgCfGfUfaUfgGfcUfa CfaAfasusu
ETD01366	9718	ususguAfgccAfuAfcgcaa ucasusu	9615	usGf saUfuGfcGfuAfuGfGcfu AfcAfasusu
ETD01367	9719	usgsuagCfCfaUfaCfGcaa ucgasusu	9616	usCfsgAfuUfgCfGfUfaUfgGfc UfaCfasusu
ETD01368	9720	csasuacGfcAfAfucgccug caasusu	9617	usUfsgCfaGfgCfGfAfuUfgCfG UfaUfgsusu
ETD01369	9721	gscsuu CfCfugCfaugaccu agasusu	9618	usCfsuAfgGfuCfaUfgCfaGfg AfaGfcsusu
ETD01370	9722	csusuccuGfCafuGfaccua gaasusu	9619	usUfscUfaGfgUfcAfuGfcAfg GfaAfgsusu
ETD01371	9723	csusucu CfagCfcCfaccu aaasusu	9620	usUfsuAfuGfgUfgGfgCfuGfa GfaAfgsusu
ETD01372	9724	cscsuccUfaUfuUfCfuac guggasusu	9621	usCfscAfcGfuAfgAfaAfuAfg GfaGfgsusu
ETD01373	9725	cscsacGfcucAfgfugucua ucasusu	9622	usGf saUfaGfaCfaCfuGfaGfc GfuGfgsusu
ETD01374	9726	csasguGfucuAfuacaggcgu casusu	9623	usGf saCfGfcUfgAfuAfgAfc AfcUfgsusu
ETD01375	9727	gsusguCfUfaUfCfaggcgu cucasusu	9624	usGf saGfaCfGfcUfgAfuAfg AfcAfcusu
ETD01376	9728	usgsucuAfuCfGfGfcgucu caasusu	9625	usUfsgAfgAfcGfcCfuGfaUfa GfaCfasusu
ETD01377	9729	gsuscuAfuCfGfGfcgucuc aaasusu	9626	usUfsuGfaGfaCfGfcUfgAfu AfgAfcusu
ETD01378	9730	usasucaGfGfcGfucucaag gcasusu	9627	usGfscCfuUfgAfgAfcGfcCfu GfaUfasusu
ETD01379	9731	usgsccCfaagCfaUfcuugu cuasusu	9628	usAfsGfCfaAfaGfaUfgCfuUfg GfgCfasusu
ETD01380	9732	csasucUfugUfCfUfCfcua caguasusu	9629	usAfsUfgUfaGfgAfgAfaCfa GfaUfgsusu
ETD01381	9733	ususguCfUfCfCfUfacagu auugasusu	9630	usCf saAfuAfcUfgUfaGfgAfg AfcAfasusu
ETD01382	9734	usgsucuccuAfcAfguaauug aasusu	9631	usUfscAfaUfaCfuGfuAfgGfa GfaCfasusu
ETD01383	9735	uscsuccuAfcAfgfuaauuga auasusu	9632	usAfsuUfcAfaUfaCfuGfuAfg GfaGfasusu
ETD01384	9736	gsusauUfgaaUfaCfGgca caasusu	9633	usUfsgUfgCfaCfGfUfaUfuCfa AfuAfcusu
ETD01385	9737	asusugaaUfaCfGfGfcaca gcasusu	9634	usGfscUfgUfgCfaCfGfUfaUfu CfaAfasusu
ETD01386	9738	ususgaAfuAfcGfuGfcaca gcuasusu	9635	usAfsGfCfuGfuGfcAfcGfuAfu UfcAfasusu
ETD01387	9739	gsasauAfcGfuGfcAfcagc uucasusu	9636	usGf saAfgCfuGfuGfcAfcGfu AfuUfcusu
ETD01388	9740	ascsuuccuGfAfcuguacag casusu	9637	usGfscUfgUfaCfaGfuCfaGfg AfaGfususu
ETD01389	9741	asgsccagagUfUfgggugac uasusu	9638	usAfsGfCfaAfcCfcAfaCfuCfu GfgCfususu
ETD01390	9742	gsgsuccucGfAfcugcagau uasusu	9639	usAfsaUfcUfgCfaGfuCfGfg GfaCfcusu
ETD01391	9743	gsusccUfCfGfCfUfgcaga uuuasusu	9640	usAfsaAfuCfuGfcAfgUfcGfa GfgAfcusu

ETD01392	9744	uscs cuCf gaCfUfgCfagau uugasusu	9641	usCf saAfaUfcUfgCfaGfuCf g AfgGfasusu
ETD01393	9745	cs csucGfAfcuGfcAfgauu ugcasusu	9642	usGf scAfaAfuCfuGfcAfgUfc GfaGfgsusu
ETD01394	9746	cs g sacUGfCfAfgauuugcu ccasusu	9643	usGf sgAfgCfaAfaUfcUfgCfa GfuCf g s u s u
ETD01395	9747	cs usgcagaUfUfugcuccaa aasusu	9644	usUf suUfgGfgAfcAfaAfuCfu GfcAfgsusu
ETD01396	9748	us gscagaUfuUfgCfuccaa aaasusu	9645	usUf suUfuGfgAfgCfaAfaUfc UfgCfasusu
ETD01397	9749	cs asgaUfuUfgCfuCfcaaa acgasusu	9646	usCf sgUfuUfuGfgAfgCfaAfa UfcUfgsusu
ETD01398	9750	gs usggagCf gCfUfguuug aaasusu	9647	usUf suCfaCfaAfcAfgCf gCfu CfcAfc s u s u
ETD01399	9751	us gsgagCf gCfUfgUfugug aauasusu	9648	usAf suUfcAfcAfaCfaGfcGfc UfcCfasusu
ETD01400	9752	cs asagGfAfcAfgCfcaaaa acuasusu	9649	usAf sgUfuUfuGfgAfgCf gUfc CfuUfgsusu
ETD01401	9753	us gsc c c cGfGfAfaAfgac uuugasusu	9650	usCf saAfaGfuCfuUfuCfcGfg GfgCfasusu
ETD01402	9754	gs csc c c cGfAfaAfgacuu uguasusu	9651	usAf scAfaAfgUfcUfuUfcCf g GfgGfc s u s u
ETD01403	9755	cs csc c c cGfAfaAfgAfcuu uguaasusu	9652	usUf saCfaAfaGfuCfuUfuCfc GfgGfg s u s u
ETD01404	9756	cs csc c cGfAfaAfgAfcuuu guagasusu	9653	usCf suAfcAfaAfgUfcUfuUfc Cf gGfg s u s u
ETD01405	9757	us usguaGfaGfGfaGfuuuug aguasusu	9654	usAf scUfcAfaAfcUfcCfuCfu AfcAfasusu
ETD01406	9758	as gsc cuCfaCfCf g u g a c u a acasusu	9655	usGf suUfaGfuCfaCf gGfuGfa GfgCf u s u s u
ETD01407	9759	cs uscaccGfuGfAfcuaaca ugasusu	9656	usCf saUfgUfuAfgUfcAfcGfg UfgAfgsusu
ETD01408	9760	us csaccGfuGfAfcuaacau gcasusu	9657	usGf scAfuGfuUfaGfuCfaCf g GfuGfasusu
ETD01409	9761	cs asccgUfgaCfUfaacaug ccasusu	9658	usGf sgCfaUfgUfuAfgUfcAfc GfgUfgsusu
ETD01410	9762	us gsc uGfAfuAfgCfAfgug caacasusu	9659	usGf suUfgCfaCfuGfcUfaUfc AfgCfasusu
ETD01411	9763	gs uscuCfaCfuCfuugaagg ccasusu	9660	usGf sgCfcUfuCfaAfgAfgUfg AfgAfc s u s u
ETD01412	9764	us csacucuuGfaAfggccag aasusu	9661	usUf scUfgGfcCfuUfcAfaGfa GfuGfasusu
ETD01413	9765	us gsu gCfUfggUfcfaaugg gacasusu	9662	usGf suCfcCfaUfuGfaCfcAfg CfaCfasusu
ETD01414	9766	gs gsu cAfaUfGfGfAfcug agugasusu	9663	usCf saCfuCfaGfuCfcCfaUfu GfaCfc s u s u
ETD01415	9767	us csaaUGfGfGfAfcugagu gucasusu	9664	usGf saCfaCfuCfaGfuCfcCfa UfuGfasusu
ETD01416	9768	cs asau g g g aCfUfgaguguc uasusu	9665	usAf sgAfcAfcUfcAfgUfcCfc AfuUfgsusu
ETD01417	9769	gs asc uGfaGfuGfucugcua gcasusu	9666	usGf scUfaGfcAfgAfcAfcUfc AfgUfc s u s u
ETD01418	9770	gs asggGfGfcaGfcuuuuau guasusu	9667	usAf scAfuAfaAfaGfcUfgCfc CfcUfc s u s u
ETD01419	9771	gs c s a g cUfUfUfUfaUfgug ccacasusu	9668	usGf suGfgCfaCfaUfaAfaAfg CfuGfc s u s u
ETD01420	9772	as gsc uUfuUfaUfgUfgcca cacasusu	9669	usGf suGfuGfgCfaCfaUfaAfa AfgCf u s u s u
ETD01421	9773	gs asagaCfCfCfUfgUfcgu gcuaasusu	9670	usUf saGfcAfcGfaCfaGfgGfu CfuUfc s u s u
ETD01422	9774	as asgacccuGfucgugcuaa asusu	9671	usUf suAfgCfaCf gAfcAfgGfg UfcUf u s u s u

ETD01423	9775	csusaagCfaUfCfagcccca acasusu	9672	usGfsuUfgGfgGfcUfgAfuGfc UfuAfgsusu
ETD01424	9776	usasagcAfuCfGfccccaa cuasusu	9673	usAfsuUfuGfgGfgCfuGfaUfg CfuUfasusu
ETD01425	9777	csusguGfGfccAfGfcaucu aacasusu	9674	usGfsuUfaGfaUfgCfuGfgCfc AfcAfgsusu
ETD01426	9778	ascsuuCAfGfCAfuGfgcac uuaasusu	9675	usUf saAfgUfgCfcAfuGfcUfg AfaGfususu
ETD01427	9779	ususcaGfcauGfGfcacua guasusu	9676	usAfsuUfaAfgUfgCfcAfuGfc UfgAfasusu
ETD01428	9780	csasgcaUfggCfaCfuuaugu gcasusu	9677	usGfscAfcUfaAfgUfgCfcAfu GfcUfgsusu
ETD01429	9781	csascuuAfuGfuGfcugucau ucasusu	9678	usGf saAfuGfaCfaGfcAfcUfa AfgUfgsusu
ETD01430	9782	usgsugUfcaUfUfccauga cgasusu	9679	usCfsgUfcAfuGfgAfaUfgAfc AfgCfasusu
ETD01431	9783	usgsucaUfUfCfCfaUfgac gggcasusu	9680	usGfscCfcGfuCfaUfgGfaAfu GfaCfasusu
ETD01432	9784	csasuuccAfuGfaCfcgggcu uaasusu	9681	usUf saAfgCfcCfcUfgAfuGfg AfaUfgsusu
ETD01433	9785	asusuccAfuGfaCfcGfggcu uagasusu	9682	usCf suAfaGfcCfcGfuCfaUfg GfaAfasusu
ETD01434	9786	usgsagGfAfgCAfuGfccau uaaasusu	9683	usUf suAfaUfgGfcAfuGfcUfc CfuCfasusu
ETD01435	9787	gscsaugCfCfaUfUfaaguu ugaasusu	9684	usUfscAfaAfcUfuAfaUfgGfc AfuGfcusu
ETD01436	9788	usasuccuGfgGfuAfgagug guasusu	9685	usAfsuCfaCfuCfuAfcCfcAfg GfaUfasusu
ETD01437	9789	usgsugcuucAfGfcuacugg uasusu	9686	usAfsuCfaGfuAfgCfuGfaAfg AfcCfasusu
ETD01438	9790	csusagUfUfCfUfUfccucc aacasusu	9687	usGfsuUfgGfgAfgGfaAfgAfa CfuAfgsusu
ETD01439	9791	usasucfGfgGfuCfuGagacu acasusu	9688	usGfsuAfgUfcAfgAfgCfcCfcg AfgUfasusu
ETD01440	9792	csascuuGfGfAfgGfuuguc uacasusu	9689	usGfsuAfgAfcAfaCfuCfcAfa AfgUfgsusu
ETD01441	9793	gsasgaAfuAfcAfuAfgacc aggasusu	9690	usCfscUfgGfuCfuAfuGfuAfu UfcUfcusu
ETD01442	9794	asusagAfccAfGfGfcccag aauasusu	9691	usAfsuUfcUfgGfgCfcUfgGfu CfuAfasusu
ETD01443	9795	gsgscccAfgAfaucgaau caasusu	9692	usUfsgGfaUfuCfGfaUfcUfg GfgCfcusu
ETD01444	9796	cscscagaaUfCfgaauccaa uasusu	9693	usAfsuUfgGfaUfuCfGfaUfc UfgGfgsusu
ETD01445	9797	csasgaAfuCfAfaucgaau guasusu	9694	usAfsuAfuUfgGfaUfuCfGfaUfc UfcUfgsusu
ETD01446	9798	asgsaaucGfaAfucaaugu gasusu	9695	usCf saCfaUfuGfgAfuUfcGfa UfuCfususu
ETD01447	9799	gsasauCfgaUfCfcaaugu gcasusu	9696	usGfscAfcAfuUfgGfaUfuCfcg AfuUfcusu
ETD01448	9800	csgsaauccAfaUfGfugcca ucasusu	9697	usGf saUfgGfcAfcAfuUfgGfa UfuCfgsusu
ETD01449	9801	gsasauCfCfaUfgUfgcca ucaasusu	9698	usUfsgAfuGfgCfaCfaUfuGfg AfuUfcusu
ETD01450	9802	csasauUfgCfCfaUfcaag ucaasusu	9699	usUfsgAfcUfuGfaUfgGfcAfc AfuUfgsusu
ETD01451	9803	usgsugCfCfaUfcaagucac uaasusu	9700	usUf saGfuGfaCfuUfgAfuGfg CfaCfasusu
ETD01452	9804	gsusgccAfuCfaAfgucacu aaasusu	9701	usUf suAfgUfgAfcUfuGfaUfg GfcAfcusu
ETD01453	9805	usgsccAfuCfaAfgucacua agasusu	9702	usCf suUfaGfuGfaCfuUfgAfu GfgCfasusu

ETD01454	9806	csasucaagUfCfaCfuaagu cgasusu	9703	usCfsgAfcUfuAfgUfgAfcUfu GfaUfgsusu
ETD01455	9807	uscsauuGfGfuAfucauguu gcasusu	9704	usGfscAfaCfaUfgAfuAfcCfa AfuGfasusu
ETD01456	9808	cscsuaUfaUfgUfgccacgg ugasusu	9705	usCfscAfcGfuGfgCfaCfaUfa UfaGfgsusu
ETD01457	9809	csusauAfuGfuGfccacggu gaasusu	9706	usUfscAfcCfGfuGfgAfcAfu AfuAfgsusu
ETD01458	9810	usasuaUfgUfgCfCfacggu gacasusu	9707	usGfsuCfaCfcGfuGfgCfaCfa UfaUfasusu
ETD01459	9811	asusaugugCfCfaCfagguga ccasusu	9708	usGfsgUfcAfcCfGfuGfgAfc AfuAfususu
ETD01460	9812	asasguuGfuGfcAfcaggg acasusu	9709	usGfsuCfcCfuGfuGfcAfcAfa AfcUfususu
ETD01461	9813	gsgsuggAfgCafgAfuagug ucasusu	9710	usGfsaCfaCfuAfuCfuGfcUfc CfaCfcusu
ETD01462	9814	asgsauagUfgUfcUfgcacu gcasusu	9711	usGfscAfgUfgCfaGfaCfaCfu AfuCfususu
ETD01463	9815	usgsaggGfAfcCafuuaugug caasusu	9712	usUfsgCfaCfaUfaAfuGfgUfc CfcCfasusu
ETD01464	9816	gsgsgaccaUfuUfaUfgugca gcasusu	9713	usGfscUfgCfaCfaUfaAfuGfg UfcCfcusu
ETD01465	9817	cscsagCfaaCfCfuacauga acasusu	9714	usGfsuUfcAfuGfuAfgGfuUfg CfuGfgsusu

[00217] Any siRNA among any of subsets A-H may comprise any modification pattern described herein. If a sequence is a different number of nucleotides in length than a modification pattern, the modification pattern may still be used with the appropriate number of additional nucleotides added 5' or 3' to match the number of nucleotides in the modification pattern. For example, if a sense or antisense strand of the siRNA among any of subsets A-F comprises 19 nucleotides, and a modification pattern comprises 21 nucleotides, UU may be added onto the 5' end of the sense or antisense strand.

Example 3: Screening MST1R siRNAs for activity in human cells in culture

[00218] Chemically modified MST1R siRNAs cross reactive for human and non-human primate and derived from sequences in siRNA subset F (**Table 8**) will be assayed for *MST1R* mRNA knockdown activity in cells in culture. A-431 (ATCC® CRL-1555™) cells will be seeded in 96-well tissue culture plates at a cell density of 10,000 cells per well in DMEM (ATCC Catalog No. 30-2002) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere composed of air plus 5% carbon dioxide. The MST1R siRNAs will be individually transfected into A-431 cells in duplicate wells at 10 nM final concentration using 0.15 µL Lipofectamine RNAiMax (Fisher) per well. Silencer Select Negative Control #1 (ThermoFisher, Catalog# 4390843) will be transfected at 10 nM final concentration as a control. After incubation for 48 hours at 37°C, total RNA will be harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of *MST1R* mRNA from each well will be measured in triplicate by real-time qPCR on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan Gene Expression Assay for human *MST1R* (ThermoFisher, assay# Hs00899921_g1). The level of *PPIA* mRNA will be measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative *MST1R* mRNA levels in each

well using the delta-delta Ct method. All data will be normalized to relative *MST1R* mRNA levels in untreated A-431 cells.

Example 4: Determining the IC50 of MST1R siRNAs

[00219] The IC50 values for knockdown of *MST1R* mRNA by select MST1R siRNAs will be determined in A-431 (ATCC® CRL-1555™) cells. The siRNAs will be assayed individually at 30 nM, 10 nM, 3 nM, 1 nM and 0.3 nM, or 3 nM, 1 nM, 0.3 nM, 0.1 nM and 0.03 nM, or 30 nM, 10 nM, 3 nM, 1 nM, 0.3 nM, 0.1 nM and 0.03 nM. The A-431 cells will be seeded in 96-well tissue culture plates at a cell density of 7,500 cells per well in DMEM (ATCC Catalog No. 30-2002) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere composed of air plus 5% carbon dioxide. The MST1R siRNAs will be individually transfected into A-431 cells in triplicate wells using 0.15 µL Lipofectamine RNAiMax (Fisher) per well. After incubation for 48 hours at 37°C, total RNA will be harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of *MST1R* mRNA from each well will be measured in triplicate by real-time qPCR on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan Gene Expression Assay for human *MST1R* (ThermoFisher, assay# Hs00899921_g1). The level of PPIA mRNA will be measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative *MST1R* mRNA levels in each well using the delta-delta Ct method. All data will be normalized to relative *MST1R* mRNA levels in untreated A-431 cells. Curve fit will be accomplished using the [inhibitor] vs. response (three parameters) function in GraphPad Prism software.

Example 5: siRNA-mediated knockdown of MST1R in A549 cell line

[00220] siRNAs targeted to *MST1R* mRNA that downregulate levels of *MST1R* mRNA may lead to a decrease in AKT activation upon MST1 protein stimulation, when administered to the cultured human lung epithelial cell line, A549.

[00221] On Day 0, A549 cells are seeded at 150,000 cells/mL into a Falcon 24-well tissue culture plate (ThermoFisher Cat. No. 353047) at 0.5 mL per well.

[00222] On Day 1, MST1R siRNA and negative control siRNA master mixes are prepared. The MST1R siRNA master mix contains 350 µL of Opti-MEM (ThermoFisher Cat. No. 4427037 - s1288 Lot No. AS02B02D) and 3.5 µL of a mixture of two MST1R siRNAs (10 µM stock). The negative control siRNA master mix contains 350 µL of Opti-MEM and 3.5 µL of negative control siRNA (ThermoFisher Cat. No. 4390843, 10 µM stock). Next, 3 µL of TransIT-X2 (Mirus Cat. No. MIR-6000) is added to each master mix. The mixes are incubated for 15 minutes to allow transfection complexes to form, then 51 µL of the appropriate master mix + TransIT-X2 is added to duplicate wells of A549 cells with a final siRNA concentration of 10 nM.

[00223] On Day 3, 48 hours post transfection, media containing MST1 protein is added and the cells are lysed 24hrs after MST1 stimulation using the Cells-to-Ct kit according to the manufacturer's protocol (ThermoFisher Cat. No. 4399002). For the Cells-to-Ct, cells are washed with 50 µL using cold 1X PBS

and lysed by adding 49.5 μ L of Lysis Solution and 0.5 μ L DNase I per well and pipetting up and down 5 times and incubating for 5 minutes at room temperature. The Stop Solution (5 μ L/well) is added to each well and mixed by pipetting up and down five times and incubating at room temperature for 2 minutes. The reverse transcriptase reaction is performed using 22.5 μ L of the lysate according to the manufacturer's protocol. Samples are stored at -80 °C until real-time qPCR is performed in triplicate using TaqMan Gene Expression Assays (Applied Biosystems FAM/MST1R using a BioRad CFX96 Cat. No. 1855195). For the protein quantification, equivalent quantities (30–50 μ g) of protein are separated by 10% SDS polyacrylamide gels and transferred to polyvinylidene fluoride membranes. Membranes are blocked with 5% nonfat milk and incubated overnight with the appropriate primary antibody at dilutions specified by the manufacturer. Next, the membranes are washed three times in TBST and incubated with the corresponding horseradish peroxidase conjugated secondary antibody at 1:5,000 dilution for 1 hr. Bound secondary antibody is detected using an enhanced chemiluminescence system. The primary immunoblotting antibodies used are anti-MST1R, anti-AKT and anti-AKT-P (Abcam, Cambridge, UK).

[00224] A decrease in *MST1R* mRNA expression in the A549 cells is expected after transfection with the MST1R siRNAs compared to *MST1R* mRNA levels in A549 cells transfected with the non-specific control siRNA 72 hours after transfection. There is also an expected decrease in the amount of activated AKT, measured by quantifying the total amount of AKT protein relative to phosphorylated AKT (AKT-P) in A549 cells transfected with the MST1R siRNAs relative to the amount of MST1R RNA containing A549 cells transfected with a non-specific control siRNA 24 hours after MST1 stimulation. These results will show that MST1R siRNAs may elicit knockdown of *MST1R* mRNA in A549 cells and that decreased MST1R expression may correspond with a decrease in activated AKT.

Example 6: ASO-mediated knockdown of *MST1R* in A549 cell line

[00225] ASOs targeted to *MST1R* mRNA that downregulate levels of *MST1R* mRNA may lead to a decrease in AKT activation upon MST1 protein stimulation, when administered to the cultured human lung epithelial cell line, A549.

[00226] On Day 0, A549 cells are seeded at 150,000 cells/mL into a Falcon 24-well tissue culture plate (ThermoFisher Cat. No. 353047) at 0.5 mL per well.

[00227] On Day 1, MST1R ASO and negative control ASO master mixes are prepared. The MST1R ASO master mix contains 350 μ L of Opti-MEM (ThermoFisher Cat. No. 4427037 - s1288 Lot No. AS02B02D) and 3.5 μ L of a mixture of the MST1R ASOs (10 μ M stock). The negative control ASO master mix contains 350 μ L of Opti-MEM and 3.5 μ L of negative control ASO (ThermoFisher Cat. No. 4390843, 10 μ M stock). Next, 3 μ L of TransIT-X2 (Mirus Cat. No. MIR-6000) is added to each master mix. The mixes are incubated for 15 minutes to allow transfection complexes to form, then 51 μ L of the appropriate master mix + TransIT-X2 is added to duplicate wells of A549 cells with a final ASO concentration of 10 nM.

[00228] On Day 3, 48 hours post transfection, media containing MST1 protein is added and the cells are lysed 24hrs after MST1 stimulation using the Cells-to-Ct kit according to the manufacturer's protocol (ThermoFisher Cat. No. 4399002). For the Cells-to-Ct, cells are washed with 50 μ L using cold 1X PBS

and lysed by adding 49.5 μ L of Lysis Solution and 0.5 μ L DNase I per well and pipetting up and down 5 times and incubating for 5 minutes at room temperature. The Stop Solution (5 μ L/well) is added to each well and mixed by pipetting up and down five times and incubating at room temperature for 2 minutes. The reverse transcriptase reaction is performed using 22.5 μ L of the lysate according to the manufacturer's protocol. Samples are stored at -80 °C until real-time qPCR is performed in triplicate using TaqMan Gene Expression Assays (Applied Biosystems FAM/MST1R using a BioRad CFX96 Cat. No. 1855195). For the protein quantification, equivalent quantities (30–50 μ g) of protein are separated by 10% SDS polyacrylamide gels and transferred to polyvinylidene fluoride membranes. Membranes are blocked with 5% nonfat milk and incubated overnight with the appropriate primary antibody at dilutions specified by the manufacturer. Next, the membranes are washed three times in TBST and incubated with the corresponding horseradish peroxidase conjugated secondary antibody at 1:5,000 dilution for 1 hr. Bound secondary antibody is detected using an enhanced chemiluminescence system. The primary immunoblotting antibodies used are anti-MST1R, anti-AKT and anti-AKT-P (Abcam, Cambridge, UK).

[00229] A decrease in *MST1R* mRNA expression in the A549 cells is expected after transfection with the MST1R ASOs compared to *MST1R* mRNA levels in A549 cells transfected with the non-specific control ASO 72 hours after transfection. There is also an expected decrease in the amount of activated AKT, measured by quantifying the total amount of AKT protein relative to phosphorylated AKT (AKT-P) in A549 cells transfected with the MST1R ASOs relative to the amount of MST1R RNA containing A549 cells transfected with a non-specific control ASO 24 hours after MST1 stimulation. These results will show that the MST1R ASOs may elicit knockdown of *MST1R mRNA* in A549 cells and that decreased MST1R expression may correspond with a decrease in activated AKT.

Example 7: Inhibition of *MST1R* in a Mouse Model of Lung Inflammation Via Acute Cigarette Smoke Exposure Using MST1R siRNAs or ASOs

[00230] In this experiment, a mouse model of lung inflammation induced by acute cigarette smoke exposure will be used to evaluate the effect of siRNA or ASO inhibition of *MST1R*. In this cigarette smoke induced model, mice are exposed to cigarette smoke for 3 hours which will result in a transient inflammatory response. Lung inflammation is assessed by measuring neutrophils and macrophages in bronchoalveolar lavage fluid and lung tissue.

[00231] Mice are divided into six groups: Group 1 - a group treated with non-targeting control siRNA and cigarette smoke inhalation, Group 2 - a group treated with non-targeting control ASO and cigarette smoke inhalation, Group 3 - a group treated with MST1R siRNA1 and cigarette smoke inhalation, Group 4 - a group treated with MST1R ASO1 and cigarette smoke inhalation, Group 5 - a group treated with vehicle and cigarette smoke inhalation, Group 6 - a group treated with vehicle and not receiving cigarette smoke stimulus. Each group contains eight mice (4 males, 4 females).

[00232] Administration of siRNA, ASO or vehicle is achieved with 10 μ g/kg of siRNA or ASO suspended in 0.9% sodium chloride (Baxter Cat. No. JB1323) delivered via inhalation using a Lovelace nebulizer (model 01-100) at a flow rate of 1 liter/min. Restrained mice are treated for a total of 10 min. Group 1 mice receive non-targeting control siRNA, Group 2 mice receive non-targeting control ASO, Group 3

mice receive siRNA1 targeting mouse *MST1R*, Group 4 mice receive ASO1 targeting mouse *MST1R*, and Group 5 and 6 mice receive vehicle.

[00233] 24 hours after the smoke inhalation treatment, bronchoalveolar lavage fluid is collected and the mice are sacrificed by cervical dislocation following an intraperitoneal injection of 0.3 ml Nembutal (5 mg/ml) (Sigma Cat. No. 1507002). Final blood samples are collected, and livers and lungs are removed, and a section placed in RNeasy lysis buffer for mRNA isolation.

[00234] mRNA is isolated from tissue placed in RNeasy lysis buffer using the PureLink kit according to the manufacturer's protocol (ThermoFisher Cat. No. 12183020). The reverse transcriptase reaction is performed according to the manufacturer's protocol. Samples are stored at -80 °C until real-time qPCR is performed in triplicate using TaqMan Gene Expression Assays (Applied Biosystems FAM/*MST1R* using a BioRad CFX96 Cat. No. 1855195).

[00235] A decrease in *MST1R* mRNA expression in the lung tissue from mice dosed with the *MST1R* siRNA1 or ASO1 is expected compared to *MST1R* mRNA expression in lung tissue from mice dosed with the non-specific controls. There is an expected decrease in neutrophil and macrophage counts in the bronchoalveolar lavage fluid in cigarette smoke exposed mice that receive the *MST1R* siRNA or ASO compared to the neutrophil and macrophage counts in the bronchoalveolar lavage fluid in cigarette smoke exposed mice that receive the non-specific control. These results will show that the *MST1R* siRNA or ASO may elicit knockdown of *MST1R* mRNA in lung tissue and that the decrease in *MST1R* expression may correspond with a decrease in neutrophil and macrophage counts in the bronchoalveolar lavage fluid in mice exposed to cigarette smoke.

Example 8: Inhibition of *MST1R* in a Mouse Model of COPD Using *MST1R* siRNAs or ASOs

[00236] In this experiment, a mouse model of cigarette smoke induced COPD will be used to evaluate the effect of siRNA or ASO inhibition of *MST1R*. In the cigarette smoke induced COPD model, mice are exposed to cigarette smoke for 6 months to mimic patients with a substantial history of cigarette smoking. Lung inflammation is assessed by measuring neutrophil and macrophage in bronchoalveolar lavage fluid and lung tissue. Lung function is also assessed by measuring tidal volume, resistance and dynamic compliance. Additionally, lung morphology and air space enlargement is assessed by fixing and staining the lungs and measuring structural parameters such as air space, septal wall thickness and mean linear intercept.

[00237] Mice are divided into six groups: Group 1 - a group treated with non-targeting control siRNA and cigarette smoke inhalation, Group 2 - a group treated with non-targeting control ASO and cigarette smoke inhalation, Group 3 - a group treated with *MST1R* siRNA1 and cigarette smoke inhalation, Group 4 - a group treated with *MST1R* ASO1 and cigarette smoke inhalation, Group 5 - a group treated with vehicle and cigarette smoke inhalation, Group 6 - a group treated with vehicle and not receiving cigarette smoke stimulus. Each group contains eight mice (4 males, 4 females).

[00238] Administration of siRNA, ASO or vehicle is achieved with 10 ug/kg of siRNA or ASO suspended in 0.9% sodium chloride (Baxter Cat. No. JB1323) delivered via inhalation using a Lovelace nebulizer (model 01-100) at a flow rate of 1 liter/min. Restrained mice are treated for a total of 10 min.

Group 1 mice receive non-targeting control siRNA, Group 2 mice receive non-targeting control ASO, Group 3 mice receive siRNA1 targeting mouse *MST1R*, Group 4 mice receive ASO1 targeting mouse *MST1R*, and Group 5 and 6 mice receive vehicle. Every 7 days after the first administration animals from each group will be dosed for a total of 12 administrations.

[00239] 24 hours after the final smoke inhalation treatment, bronchoalveolar lavage fluid is collected and the mice are sacrificed by cervical dislocation following an intraperitoneal injection of 0.3 ml Nembutal (5 mg/ml) (Sigma Cat. No. 1507002). Final blood samples are collected, and livers and lungs are removed, and a section placed in RNAlater for mRNA isolation or fixed with paraformaldehyde and then embedded in paraffin for tissue sectioning.

[00240] mRNA is isolated from tissue placed in RNAlater solution using the PureLink kit according to the manufacturer's protocol (ThermoFisher Cat. No. 12183020). The reverse transcriptase reaction is performed according to the manufacturer's protocol. Samples are stored at -80 °C until real-time qPCR is performed in triplicate using TaqMan Gene Expression Assays (Applied Biosystems FAM/*MST1R* using a BioRad CFX96 Cat. No. 1855195).

[00241] A decrease in *MST1R* mRNA expression in the lung tissue from mice dosed with the *MST1R* siRNA1 or ASO1 is expected compared to *MST1R* mRNA expression in the lung tissue from mice dosed with the non-specific controls. There is an expected decrease in neutrophil and macrophage counts in the bronchoalveolar lavage fluid in cigarette smoke exposed mice that receive the *MST1R* siRNA or ASO compared to the neutrophil and macrophage counts in the bronchoalveolar lavage fluid in cigarette smoke exposed mice that receive the non-specific control. There is also an expected decrease in air space and mean linear intercept and an increase in septal wall thickness in cigarette smoke exposed mice that receive the *MST1R* siRNA or ASO compared to the air space, mean linear intercept and septal wall thickness in cigarette smoke exposed mice that receive the non-specific control. Additionally, there is also an expected decrease in compliance and tidal volume and an increase in resistance in cigarette smoke exposed mice that receive the *MST1R* siRNA or ASO compared to the compliance, tidal volume and resistance in cigarette smoke exposed mice that receive the non-specific control. These results will show that an *MST1R* siRNA or ASO may elicit knockdown of *MST1R* mRNA in lung and that the decrease in *MST1R* expression may correspond with a decrease in neutrophil and macrophage counts in the bronchoalveolar lavage fluid and increased lung function and decreased pathology in mice exposed to cigarette smoke.

Example 9: Oligonucleotide Synthesis

[00242] Oligonucleotides such as siRNAs may be synthesized according to phosphoramidite technology on a solid phase. For example, a K&A oligonucleotide synthesizer may be used. Syntheses may be performed on a solid support made of controlled pore glass (CPG, 500 Å or 600 Å, obtained from AM Chemicals, Oceanside, CA, USA). All 2'-OMe and 2'-F phosphoramidites may be purchased from Hongene Biotech (Union City, CA, USA). All phosphoramidites may be dissolved in anhydrous acetonitrile (100 mM) and molecular sieves (3 Å) may be added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) may be used as activator solution. Coupling times may be 9-18 min (e.g. with a GalNAc such as ETL17), 6 min (e.g. with 2'OMe

and 2'F). In order to introduce phosphorothioate linkages, a 100 mM solution of 3-phenyl 1,2,4-dithiazoline-5-one (POS, obtained from PolyOrg, Inc., Leominster, Mass., USA) in anhydrous acetonitrile may be employed.

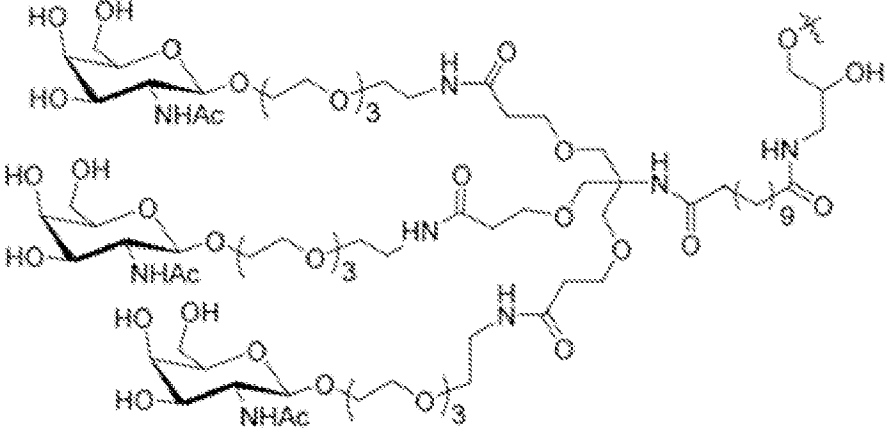
[00243] After solid phase synthesis, the dried solid support may be treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution (Aldrich) for two hours at 30° C. The solution may be evaporated and the solid residue may be reconstituted in water and purified by anionic exchange HPLC using a TKSgel SuperQ-5PW 13u column. Buffer A may be 20 mM Tris, 5 mM EDTA, pH 9.0 and contained 20% Acetonitrile and buffer B may be the same as buffer A with the addition of 1 M sodium chloride. UV traces at 260 nm may be recorded. Appropriate fractions may be pooled then desalted using Sephadex G-25 medium.

[00244] Equimolar amounts of sense and antisense strand may be combined to prepare a duplex. The duplex solution may be prepared in 0.1×PBS (Phosphate-Buffered Saline, 1×, Gibco). The duplex solution may be annealed at 95° C. for 5 min, and cooled to room temperature slowly. Duplex concentration may be determined by measuring the solution absorbance on a UV-Vis spectrometer at 260 nm in 0.1×PBS. For some experiments, a conversion factor may be calculated from an experimentally determined extinction coefficient.

Example 10: GalNAc ligand for hepatocyte targeting of oligonucleotides

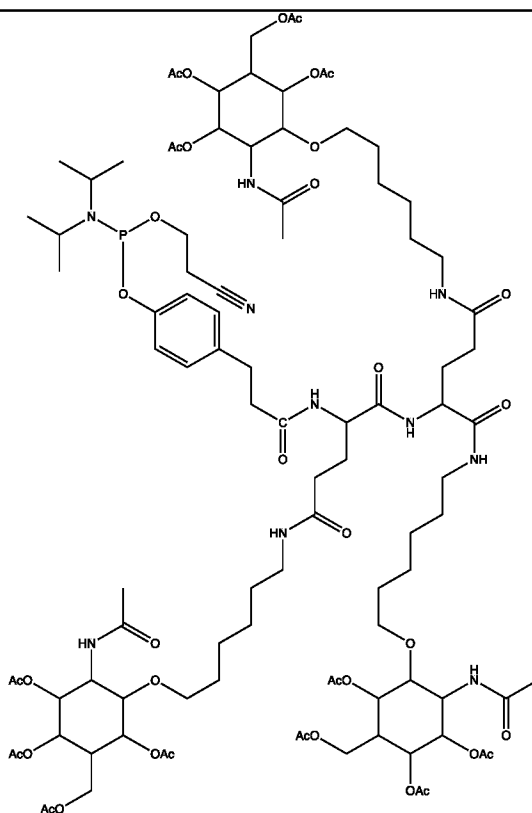
[00245] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. Reagents for GalNAc conjugation to oligonucleotides are shown in **Table 11**.

Table 11. GalNAc Conjugation Reagents

Type of conjugation	Structure
<u>Solid phase 3' attachment</u> where squiggly line is rest of oligonucleotide chain and right-most OH is where attachment to solid phase is.	 This GalNAc ligand may be referred to as "GalNAc23" or "GalNAc#23."

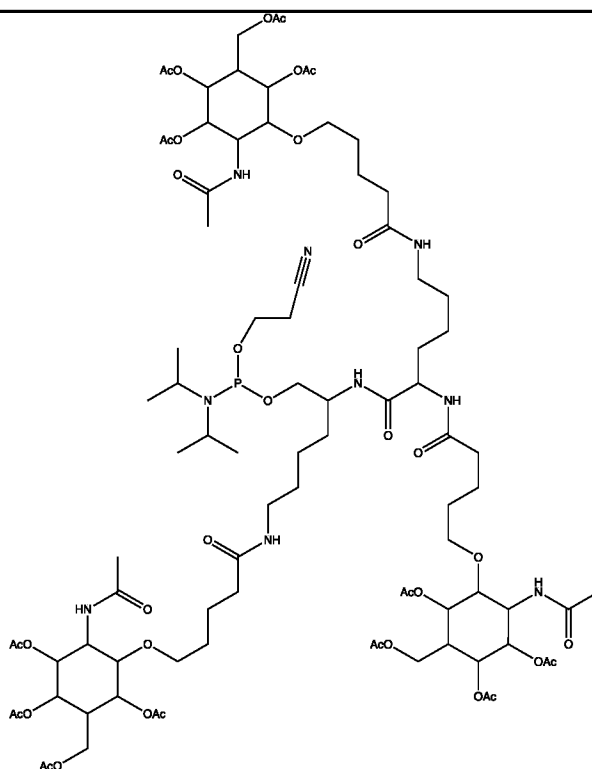
Solid phase 5'
attachment

phosphoramidite



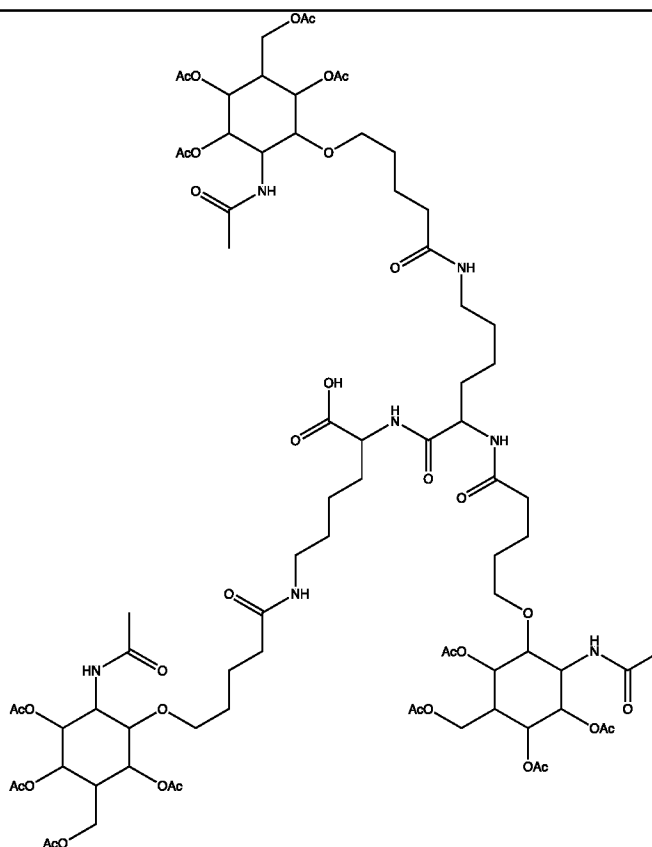
Solid phase 5'
attachment

Phosphoramidite



Solution phase

Carboxylic acid for
amide coupling
anywhere on
oligonucleotide



Where Ac is an acetyl group or other hydroxyl protecting group that can be removed under basic, acid or reducing conditions.

[00246] In solution phase conjugation, the oligonucleotide sequence—including a reactive conjugation site—is formed on the resin. The oligonucleotide is then removed from the resin and GalNAc is conjugated to the reactive site.

[00247] The carboxy GalNAc derivatives may be coupled to amino-modified oligonucleotides. The peptide coupling conditions are known to the skilled in the art using a carbodiimide coupling agent like DCC (N,N'-Dicyclohexylcarbodiimide), EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide) or EDC.HCl (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) and an additive like HOBt (1-hydroxybenzotriazole), HOSu (N-hydroxysuccinimide), TBTU (N,N,N',N'-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or HOAt (1-Hydroxy-7-azabenzotriazole) and common combinations thereof such as TBTU/HOBt or HBTU/HOAt to form activated amine-reactive esters.

[00248] Amine groups may be incorporated into oligonucleotides using a number of known, commercially available reagents at the 5' terminus, 3' terminus or anywhere in between.

[00249] Non-limiting examples of reagents for oligonucleotide synthesis to incorporate an amino group include:

- 5' attachment:
- 6-(4-Monomethoxytritylamino)hexyl-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite CAS Number: 114616-27-2

- 5'-Amino-Modifier TEG CE-Phosphoramidite
- 10-(O-trifluoroacetamido-N-ethyl)-triethyleneglycol-1-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite
- 3' attachment:
- 3'-Amino-Modifier Serinol CPG
- 3-Dimethoxytrityloxy-2-(3-(fluorenylmethoxycarbonylamino)propanamido)propyl-1-O-succinyl-long chain alkylamino-CPG (where CPG stands for controlled-pore glass and is the solid support)
- Amino-Modifier Serinol Phosphoramidite
- 3-Dimethoxytrityloxy-2-(3-(fluorenylmethoxycarbonylamino)propanamido)propyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite

[00250] Internal (base modified):

- Amino-Modifier C6 dT
- 5'-Dimethoxytrityl-5-[N-(trifluoroacetylaminohexyl)-3-acrylimido]-2'-deoxy Uridine, 3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite. CAS Number: 178925-21-8

[00251] Solution phase conjugations may occur after oligonucleotide synthesis via reactions between non-nucleosidic nucleophilic functional groups that are attached to the oligonucleotide and electrophilic GalNAc reagents. Examples of nucleophilic groups include amines and thiols, and examples of electrophilic reagents include activated esters (e.g. N-hydroxysuccinimide, pentafluorophenyl) and maleimides.

Example 11: GalNAc ligands for hepatocyte targeting of oligonucleotides

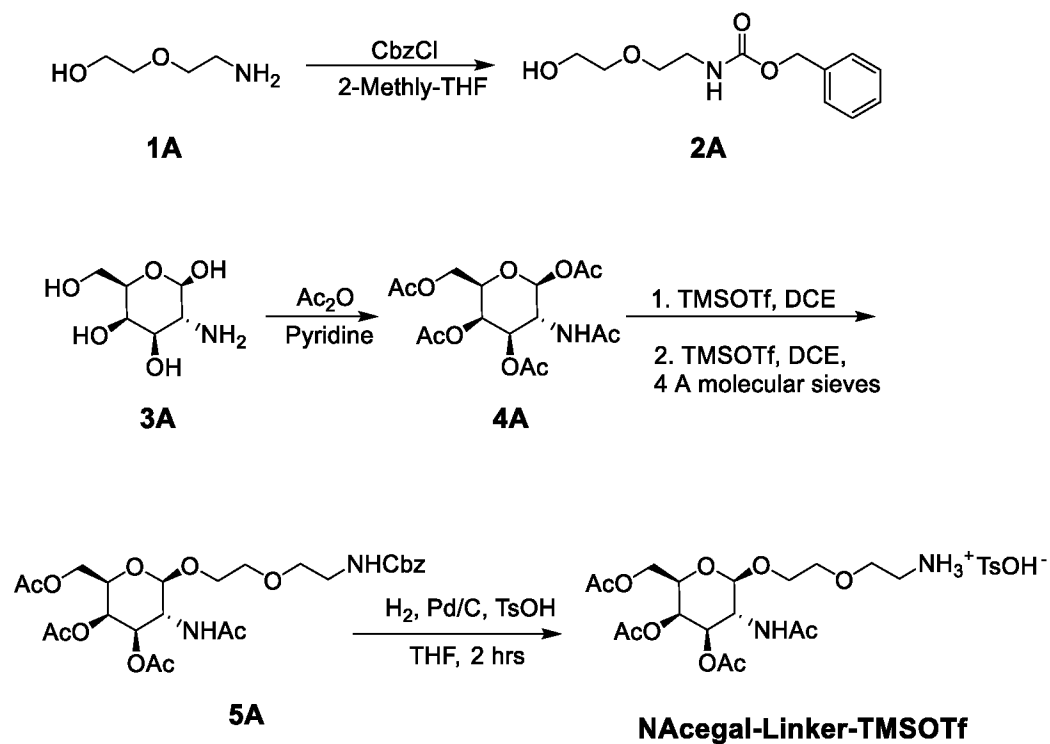
[00252] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. A non-limiting example of a phosphoramidite reagent for GalNAc conjugation to a 5' end oligonucleotide is shown in **Table 12**.

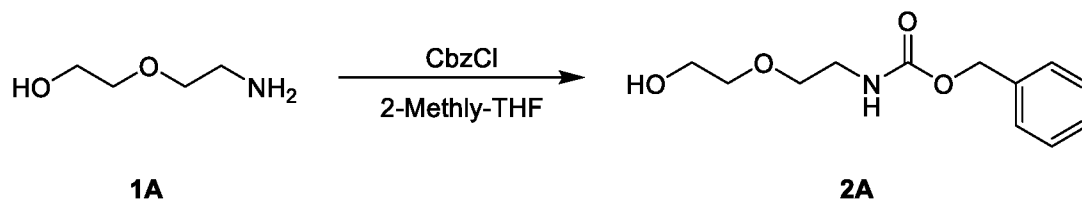
Table 12. GalNAc Conjugation Reagent

Type of conjugation	Structure
<u>Solid phase 5' attachment</u> phosphoramidite	

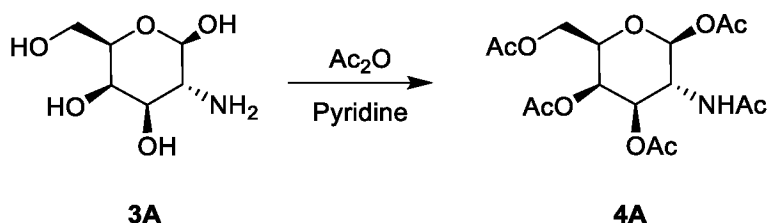
[00253] The following includes examples of synthesis reactions used to create a GalNAc moiety:

Scheme for the preparation of NAcegal-Linker-TMSOTf

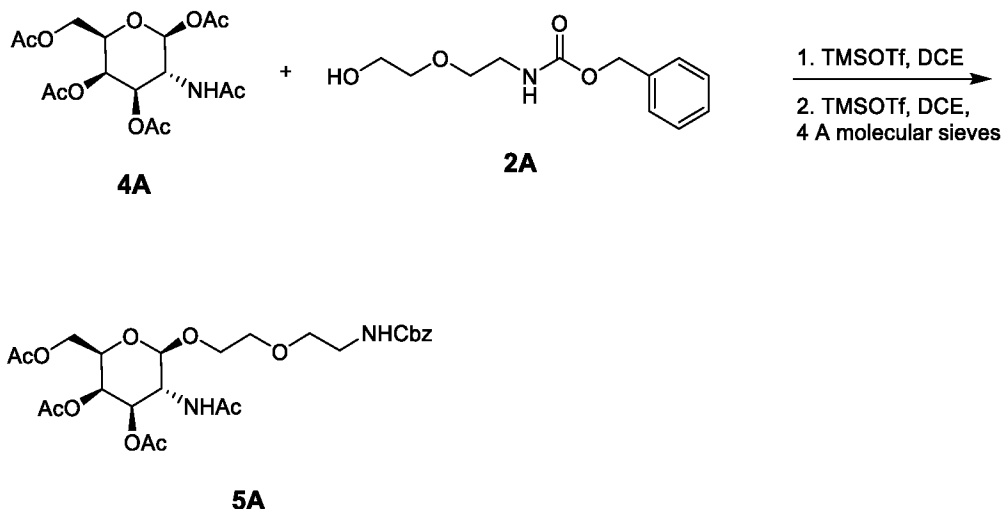


General procedure for preparation of Compound 2A

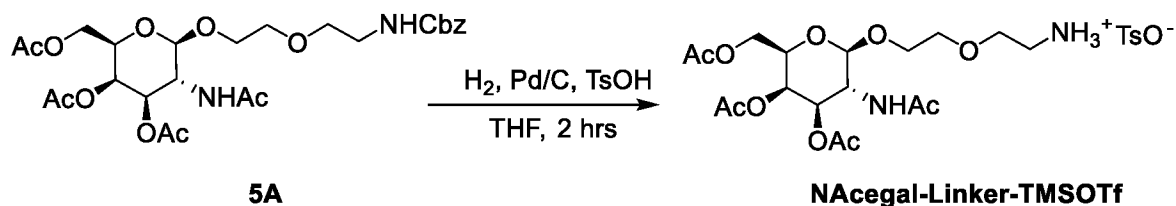
[00254] To a solution of Compound 1A (500 g, 4.76 mol, 476 mL) in 2-Methyl-THF (2.00 L) is added CbzCl (406 g, 2.38 mol, 338 mL) in 2-Methyl-THF (750 mL) dropwise at 0 °C. The mixture is stirred at 25 °C for 2 hrs under N₂ atmosphere. TLC (DCM: MeOH = 20:1, PMA) may indicate CbzCl is consumed completely and one new spot ($R_f = 0.43$) formed. The reaction mixture is added HCl/EtOAc (1 N, 180 mL) and stirred for 30 mins, white solid is removed by filtration through celite, the filtrate is concentrated under vacuum to give Compound 2A (540 g, 2.26 mol, 47.5% yield) as a pale yellow oil and used into the next step without further purification. ¹H NMR: δ 7.28 - 7.41 (m, 5 H), 5.55 (br s, 1 H), 5.01 - 5.22 (m, 2 H), 3.63 - 3.80 (m, 2 H), 3.46 - 3.59 (m, 4 H), 3.29 - 3.44 (m, 2 H), 2.83 - 3.02 (m, 1 H).

General procedure for preparation of Compound 4A

[00255] To a solution of Compound 3A (1.00 kg, 4.64 mol, HCl) in pyridine (5.00 L) is added acetyl acetate (4.73 kg, 46.4 mol, 4.34 L) dropwise at 0 °C under N₂ atmosphere. The mixture is stirred at 25 °C for 16 hrs under N₂ atmosphere. TLC (DCM: MeOH = 20:1, PMA) indicated Compound 3A is consumed completely and two new spots ($R_f = 0.35$) formed. The reaction mixture is added to cold water (30.0 L) and stirred at 0 °C for 0.5 hr, white solid formed, filtered and dried to give Compound 4A (1.55 kg, 3.98 mol, 85.8% yield) as a white solid and used in the next step without further purification. ¹H NMR: δ 7.90 (d, $J = 9.29$ Hz, 1 H), 5.64 (d, $J = 8.78$ Hz, 1 H), 5.26 (d, $J = 3.01$ Hz, 1 H), 5.06 (dd, $J = 11.29, 3.26$ Hz, 1 H), 4.22 (t, $J = 6.15$ Hz, 1 H), 3.95 - 4.16 (m, 3 H), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.90 (s, 3 H), 1.78 (s, 3 H).

General procedure for preparation of Compound 5A

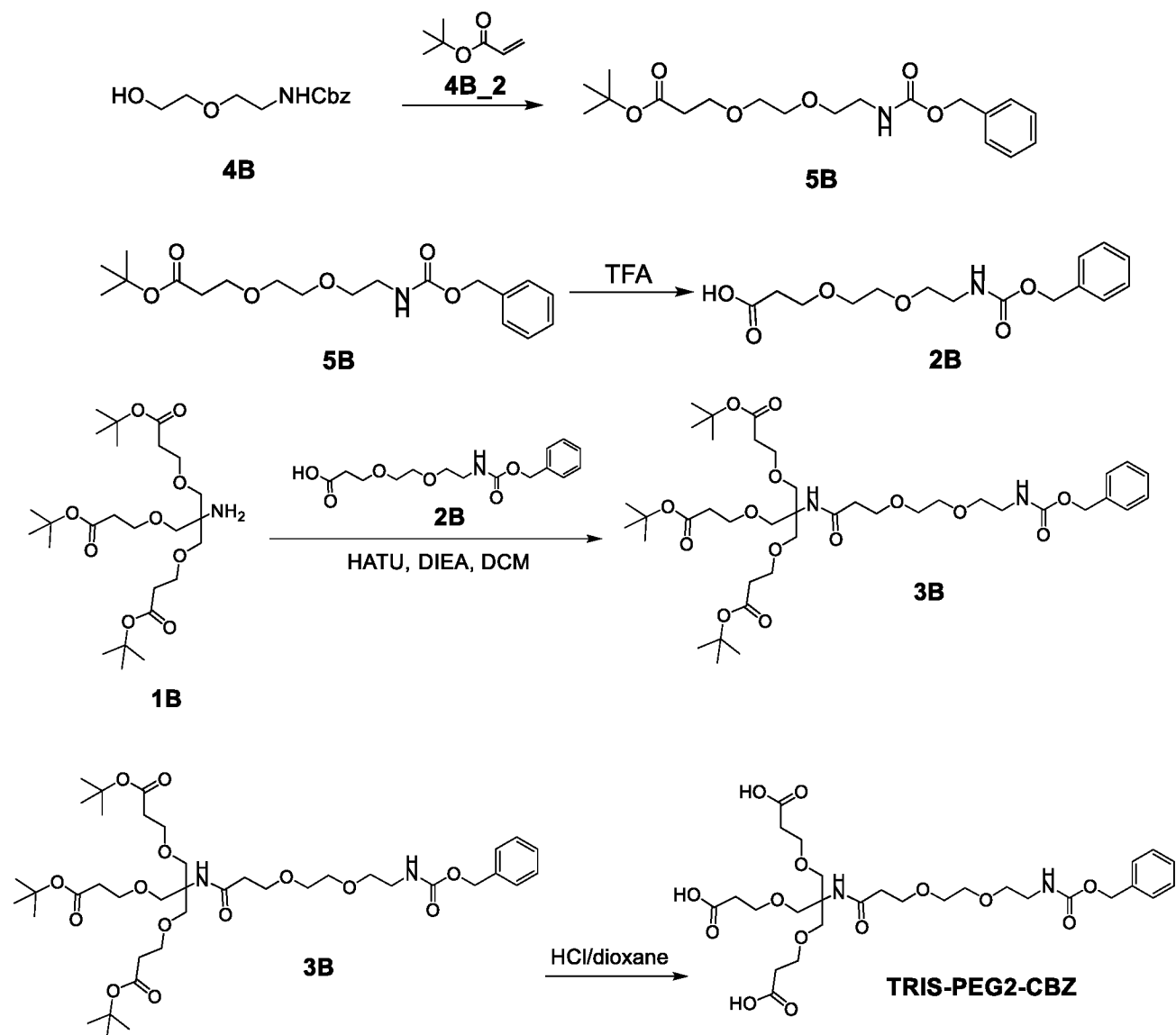
[00256] To a solution of Compound 4A (300 g, 771 mmol) in DCE (1.50 L) is added TMSOTf (257 g, 1.16 mol, 209 mL) and stirred for 2 hrs at 60 °C, and then stirred for 1 hr at 25 °C. Compound 2A (203 g, 848 mmol) is dissolved in DCE (1.50 L) and added 4 Å powder molecular sieves (150 g) stirring for 30 mins under N₂ atmosphere. Then the solution of Compound 4A in DCE is added dropwise to the mixture at 0 °C. The mixture is stirred at 25 °C for 16 hrs under N₂ atmosphere. TLC (DCM: MeOH = 25:1, PMA) indicated Compound 4A is consumed completely and new spot (R_f = 0.24) formed. The reaction mixture is filtered and washed with sat. NaHCO₃ (2.00 L), water (2.00 L) and sat. brine (2.00 L). The organic layer is dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is triturated with 2-Me-THE/heptane (5/3, v/v, 1.80 L) for 2 hrs, filtered and dried to give Compound 5A (225 g, 389 mmol, 50.3% yield, 98.4% purity) as a white solid. ¹H NMR: δ 7.81 (d, J = 9.29 Hz, 1 H), 7.20 - 7.42 (m, 6 H), 5.21 (d, J = 3.26 Hz, 1 H), 4.92 - 5.05 (m, 3 H), 4.55 (d, J = 8.28 Hz, 1 H), 3.98 - 4.07 (m, 3 H), 3.82 - 3.93 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.55 - 3.62 (m, 1 H), 3.43 - 3.53 (m, 2 H), 3.37 - 3.43 (m, 2 H), 3.14 (q, J = 5.77 Hz, 2 H), 2.10 (s, 3 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 1.77 (s, 3 H).

General procedure for preparation of NAcgal-Linker-Tosylate salt

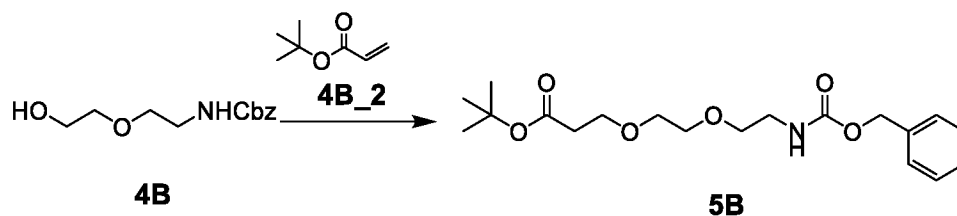
[00257] To a solution of Compound 5A (200 g, 352 mmol) in THF (1.0 L) is added dry Pd/C (15.0 g, 10% purity) and TsOH (60.6 g, 352 mmol) under N₂ atmosphere. The suspension is degassed under vacuum and purged with H₂ several times. The mixture is stirred at 25 °C for 3 hrs under H₂ (45 psi) atmosphere. TLC (DCM: MeOH = 10:1, PMA) indicated Compound 5A is consumed completely and one new spot (R_f = 0.04) is formed. The reaction mixture is filtered and concentrated ($\leq$ 40 °C) under reduced pressure to give a residue. Diluted with anhydrous DCM (500 mL, dried overnight with 4 Å molecular sieves (dried

at 300 °C for 12 hrs)) and concentrate to give a residue and run Karl Fisher (KF) to check for water content. This is repeated 3 times with anhydrous DCM (500 mL) dilutions and concentration to give NAcegal-Linker-TMSOTf (205 g, 95.8% yield, TsOH salt) as a foamy white solid. ^1H NMR: δ 7.91 (d, J = 9.03 Hz, 1 H), 7.53 - 7.86 (m, 2 H), 7.49 (d, J = 8.03 Hz, 2 H), 7.13 (d, J = 8.03 Hz, 2 H), 5.22 (d, J = 3.26 Hz, 1 H), 4.98 (dd, J = 11.29, 3.26 Hz, 1 H), 4.57 (d, J = 8.53 Hz, 1 H), 3.99 - 4.05 (m, 3 H), 3.87 - 3.94 (m, 1 H), 3.79 - 3.85 (m, 1 H), 3.51 - 3.62 (m, 5 H), 2.96 (br t, J = 5.14 Hz, 2 H), 2.29 (s, 3 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.89 (s, 3 H), 1.78 (s, 3 H).

Scheme for the preparation of TRIS-PEG2-CBZ



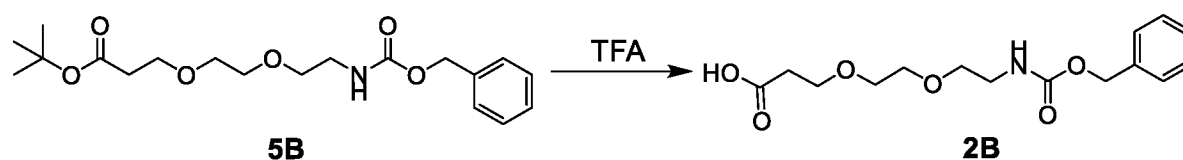
General procedure for preparation of Compound 5B



[00258] To a solution of Compound **4B** (400 g, 1.67 mol, 1.00 eq) and NaOH (10 M, 16.7 mL, 0.10 eq) in THF (2.00 L) is added Compound **4B_2** (1.07 kg, 8.36 mol, 1.20 L, 5.00 eq), the mixture is stirred at 30

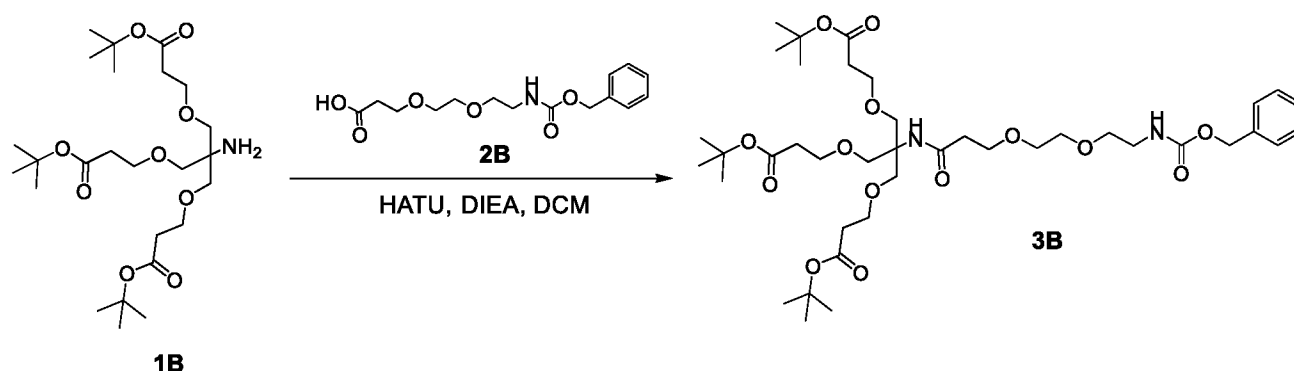
°C for 2 hrs. LCMS showed the desired MS is given. Five batches of solution are combined to one batch, then the mixture is diluted with water (6.00 L), extracted with ethyl acetate (3.00 L*3), the combined organic layer is washed with brine (3.00 L), dried over Na₂SO₄, filtered and concentrated under vacuum. The crude is purified by column chromatography (SiO₂, petroleum ether : ethyl acetate=100:1-10:1, R_f=0.5) to give Compound 5B (2.36 kg, 6.43 mol, 76.9% yield) as light yellow oil. HNMR: δ 7.31-7.36 (m, 5 H), 5.38 (s, 1 H), 5.11-5.16 (m, 2 H), 3.75 (t, J=6.4 Hz), 3.54-3.62 (m, 6 H), 3.39 (d, J=5.2 Hz), 2.61 (t, J=6.0 Hz).

General procedure for preparation of 3-oxo-1-phenyl-2,7,10-trioxa-4-azatridecan-13-oic acid (Compound 2B below)



[00259] To a solution of Compound 5B (741 g, 2.02 mol, 1.00 eq) in DCM (2.80 L) is added TFA (1.43 kg, 12.5 mol, 928 mL, 6.22 eq), the mixture is stirred at 25 °C for 3 hrs. LCMS showed the desired MS is given. The mixture is diluted with DCM (5.00 L), washed with water (3.00 L*3), brine (2.00 L), the combined organic layer is dried over Na₂SO₄, filtered and concentrated under vacuum to give Compound 2B (1800 g, crude) as light yellow oil. HNMR: δ 9.46 (s, 5 H), 7.27-7.34 (m, 5 H), 6.50-6.65 (m, 1 H), 5.71 (s, 1 H), 5.10-5.15 (m, 2 H), 3.68-3.70 (m, 14 H), 3.58-3.61 (m, 6 H), 3.39 (s, 2 H), 2.55 (s, 6 H), 2.44 (s, 2 H).

General procedure for preparation of Compound 3B



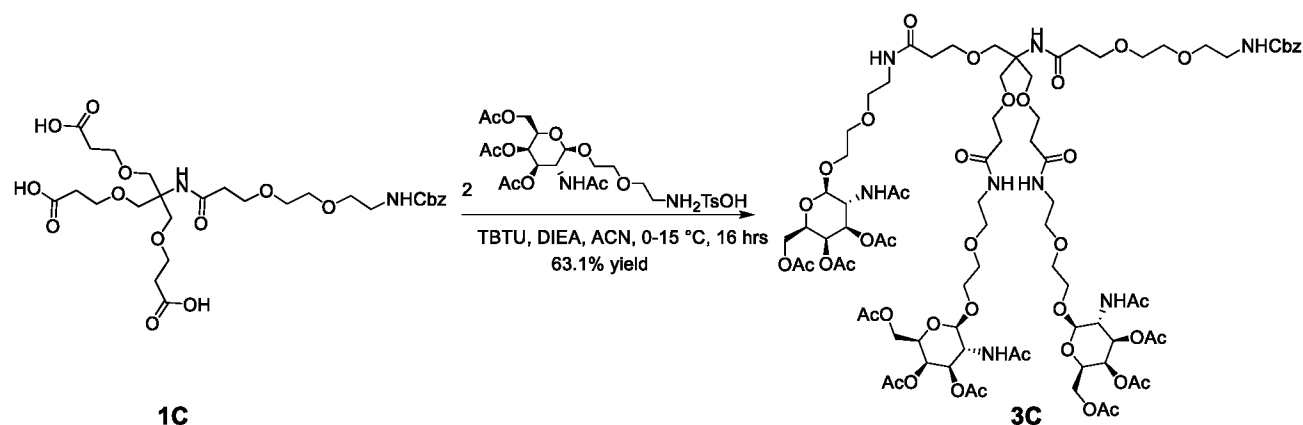
[00260] To a solution of Compound 2B (375 g, 999 mmol, 83.0% purity, 1.00 eq) in DCM (1.80 L) is added HATU (570 g, 1.50 mol, 1.50 eq) and DIEA (258 g, 2.00 mol, 348 mL, 2.00 eq) at 0 °C, the mixture is stirred at 0 °C for 30 min, then Compound 1B (606 g, 1.20 mol, 1.20 eq) is added, the mixture is stirred at 25 °C for 1 hr. LCMS showed desired MS is given. The mixture is combined to one batch, then the mixture is diluted with DCM (5.00 L), washed with 1 N HCl aqueous solution (2.00 L*2), then the organic layer is washed with saturated Na₂CO₃ aqueous solution (2.00 L *2) and brine (2.00 L), the organic layer is dried over Na₂SO₄, filtered and concentrated under vacuum to give Compound 3B (3.88 kg, crude) as yellow oil.

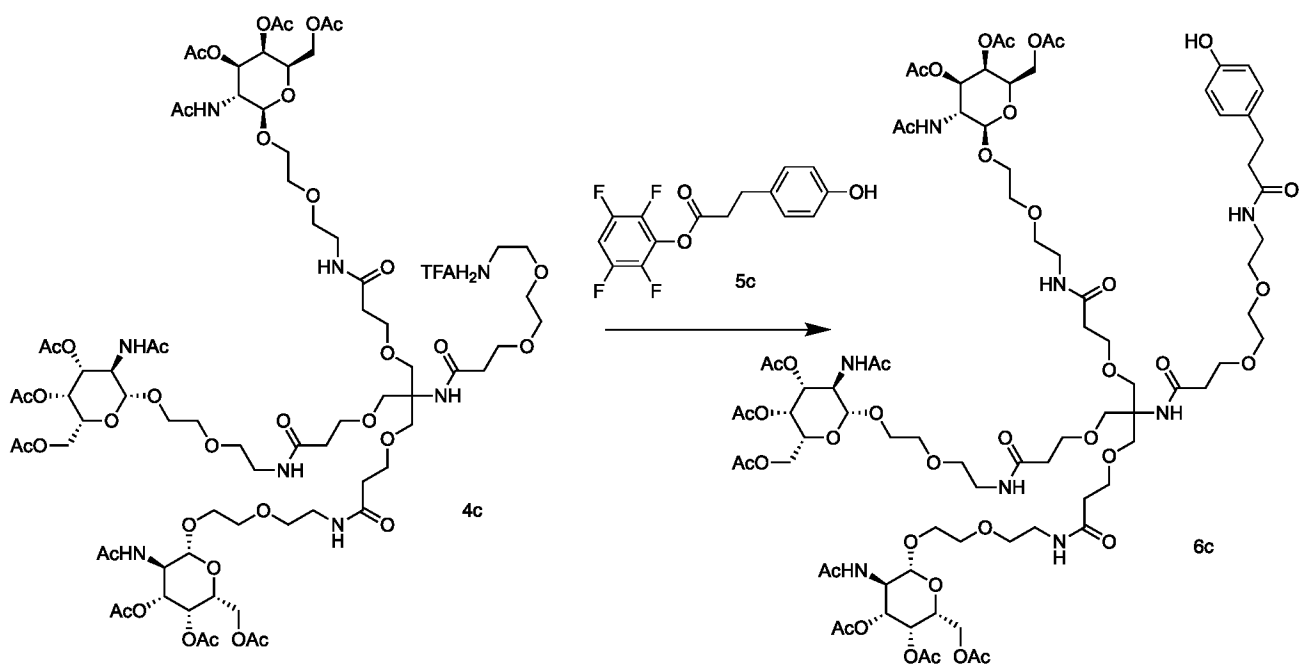
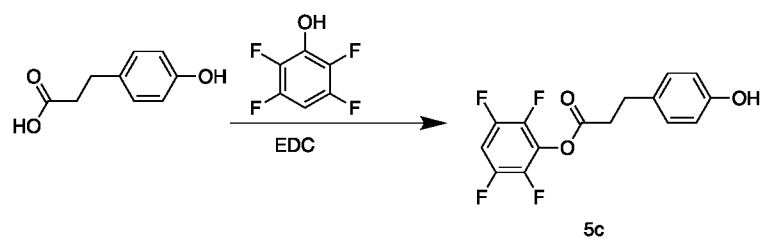
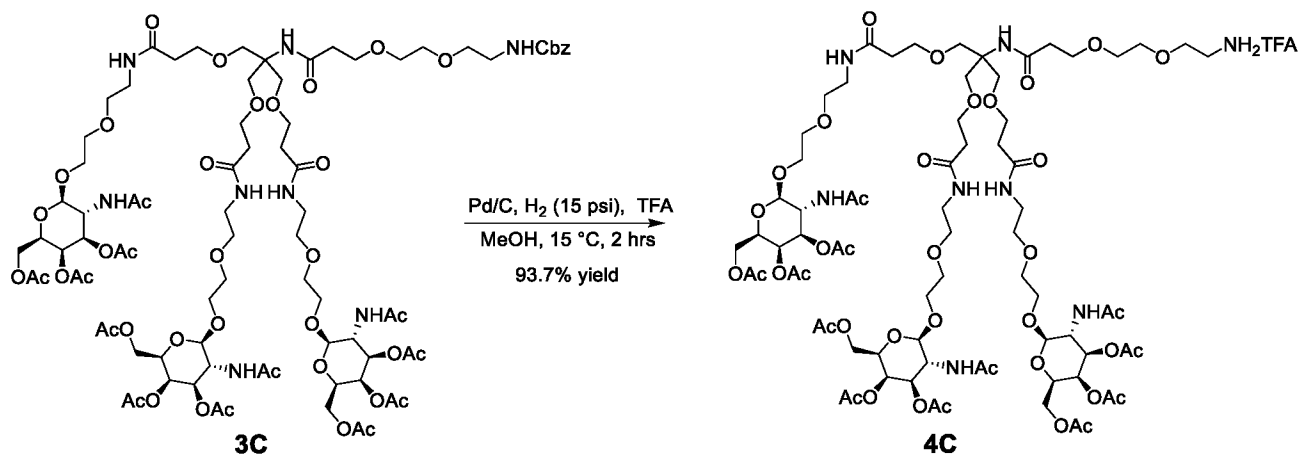
Chemical reaction scheme showing the conversion of compound **3B** to **TRIS-PEG2-CBZ**. The reaction is catalyzed by **HCl/dioxane**.

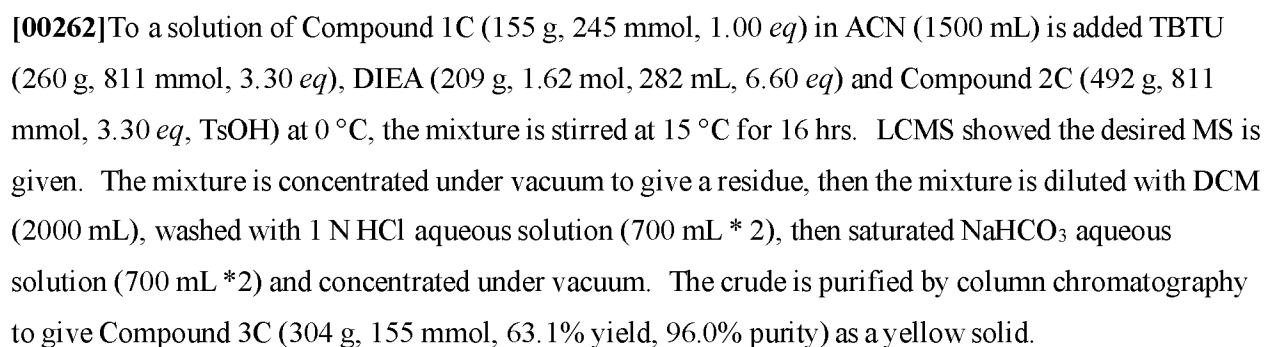
Structure of **3B**: A tri-tert-butoxy-protected intermediate. It features a central nitrogen atom bonded to a PEG chain (HO-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-NH-) and three tert-butoxy-protected carboxylic acid groups. The PEG chain is further functionalized with a CBZ (carboxybenzyl) group.

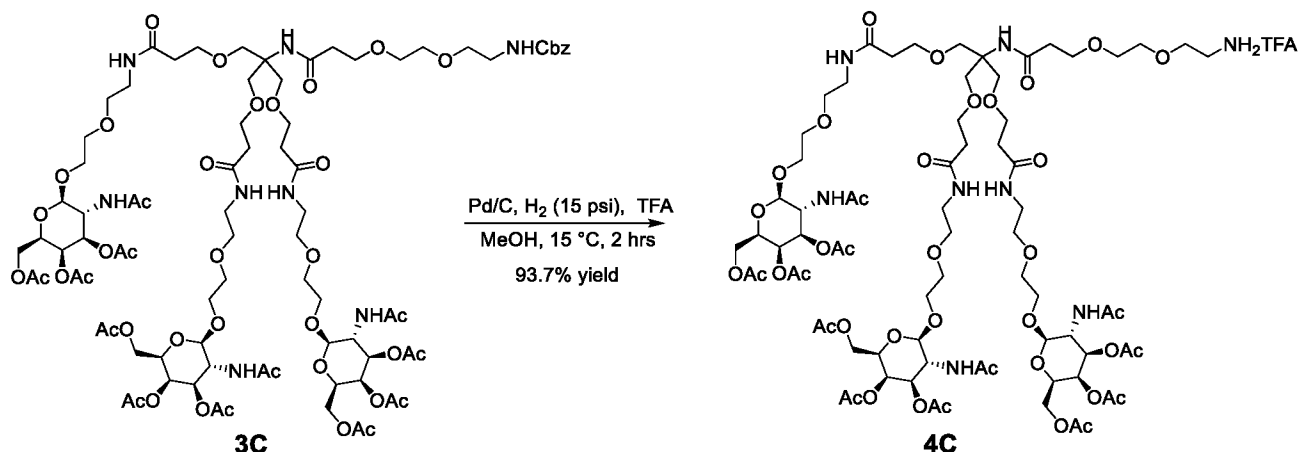
Structure of **TRIS-PEG2-CBZ**: The product of the deprotection reaction, where the tert-butoxy groups have been removed, resulting in three free carboxylic acid groups.

Scheme for the preparation of TriNGal-TRIS-Peg2-Phosph 8c

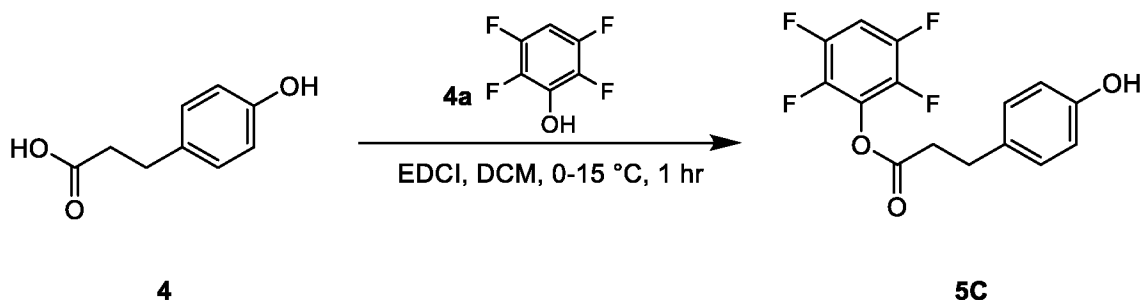






General procedure for preparation of Compound 4C

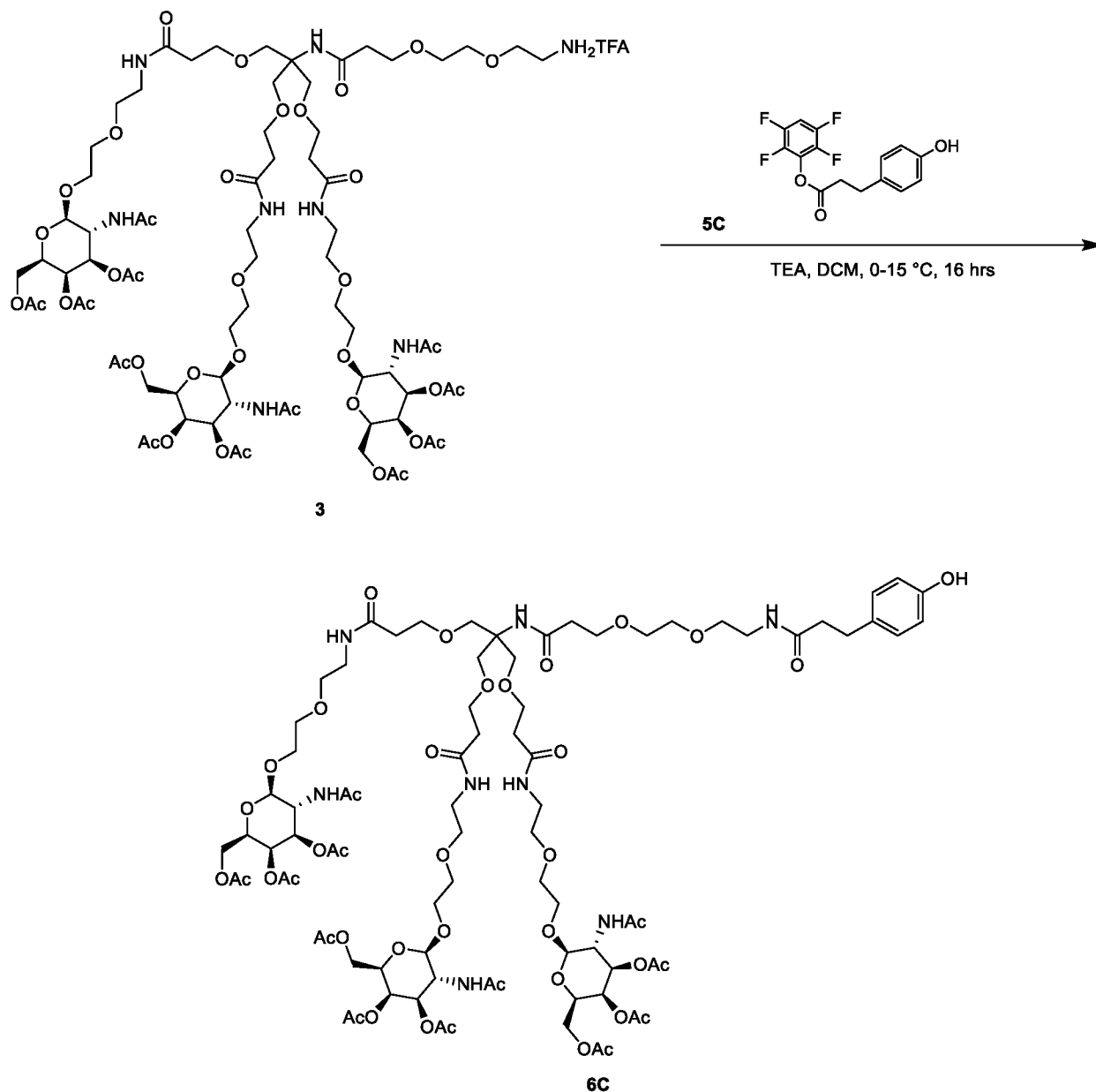
[00263] Two batches solution of Compound 3C (55.0 g, 29.2 mmol, 1.00 eq) in MeOH (1600 mL) is added Pd/C (6.60 g, 19.1 mmol, 10.0 % purity) and TFA (3.34 g, 29.2 mmol, 2.17 mL, 1.00 eq), the mixture is degassed under vacuum and purged with H₂. The mixture is stirred under H₂ (15 psi) at 15 °C for 2 hours. LCMS showed the desired MS is given. The mixture is filtered and the filtrate is concentrated under vacuum to give Compound 4C (106 g, 54.8 mmol, 93.7% yield, 96.2% purity, TFA) as a white solid.

General procedure for preparation of compound 5C

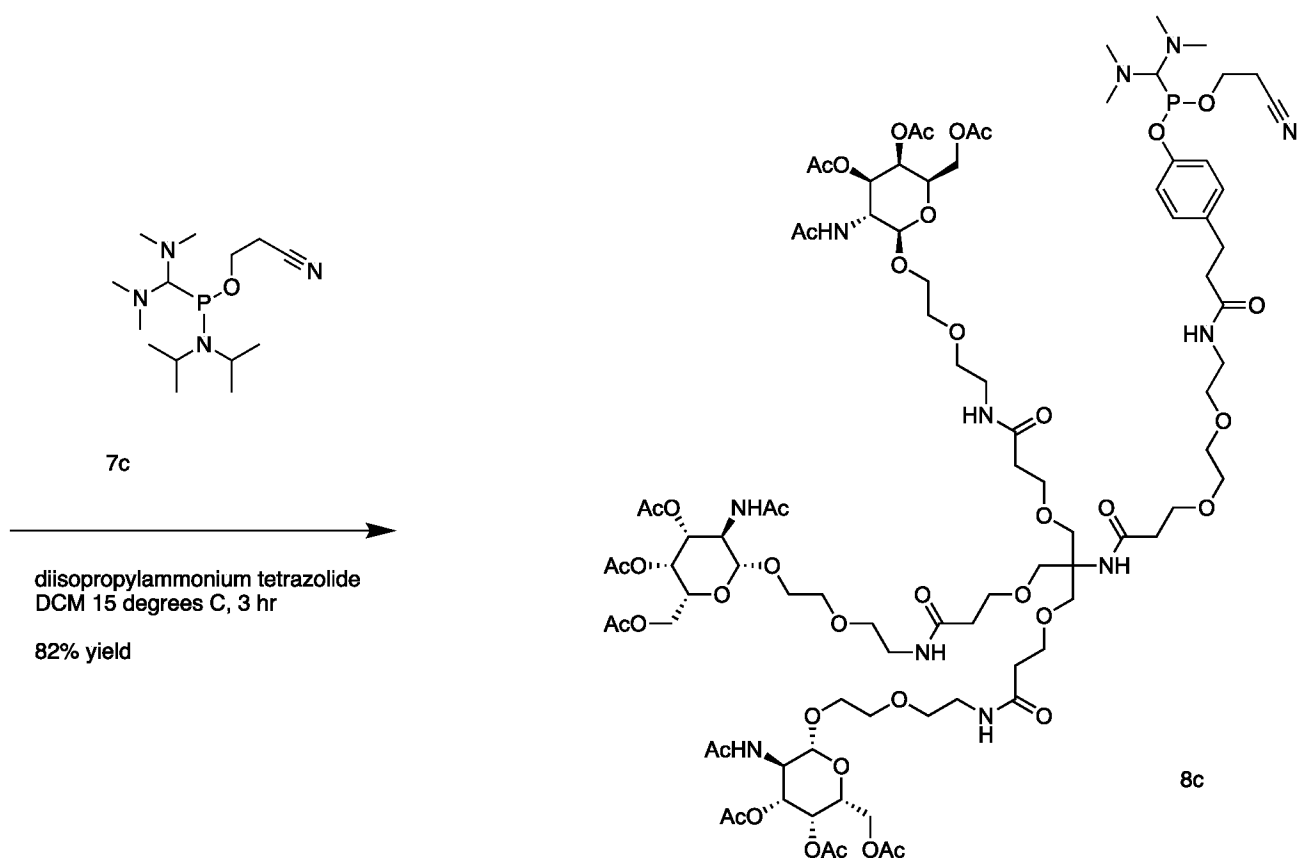
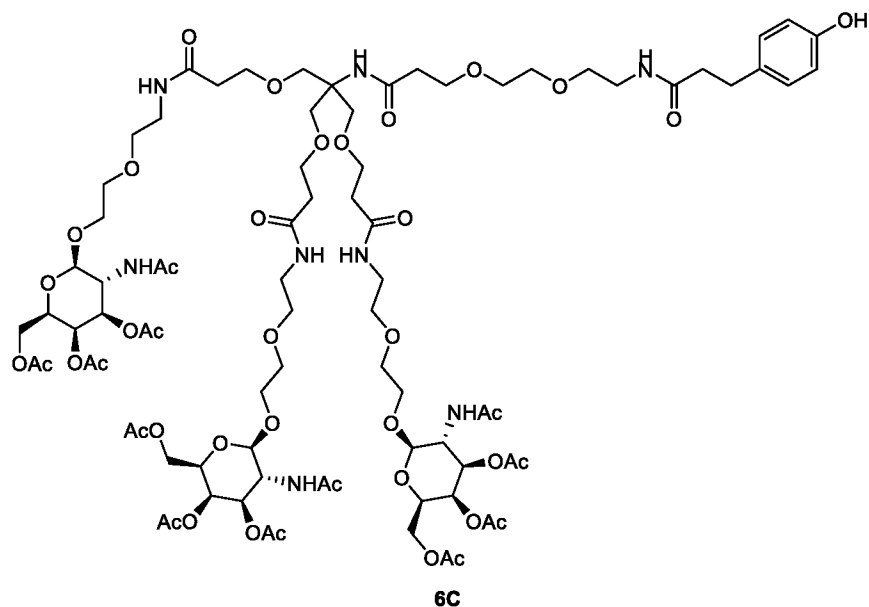
[00264] Two batches in parallel. To a solution of EDCI (28.8 g, 150 mmol, 1.00 eq) in DCM (125 mL) is added compound 4a (25.0 g, 150 mmol, 1.00 eq) dropwise at 0 °C, then the mixture is added to compound 4 (25.0 g, 150 mmol, 1.00 eq) in DCM (125 mL) at 0 °C, then the mixture is stirred at 25 °C for 1 hr.

TLC (Petroleum ether : Ethyl acetate = 3 : 1, R_f = 0.45) showed the reactant is consumed and one new spot is formed. The reaction mixture is diluted with DCM (100 mL) then washed with aq. NaHCO₃ (250 mL * 1) and brine (250 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is purified by column chromatography (SiO₂, Petroleum ether : Ethyl acetate = 100 : 1 to 3 : 1), TLC (SiO₂, Petroleum ether : Ethyl acetate = 3:1), R_f = 0.45, then concentrated under reduced pressure to give a residue. Compound 5C (57.0 g, 176 mmol, 58.4% yield, 96.9% purity) is obtained as colorless oil and confirmed ¹HNMR: EW33072-2-P1A, 400 MHz, DMSO

δ 9.21 (s, 1 H), 7.07-7.09 (m, 2 H), 6.67-6.70 (m, 2 H), 3.02-3.04 (m, 2 H), 2.86-2.90 (m, 2 H)

General procedure for preparation of compound 6

[00265] To a mixture of compound **3** (79.0 g, 41.0 mmol, 96.4% purity, 1.00 eq, TFA) and compound **6C** (14.2 g, 43.8 mmol, 96.9% purity, 1.07 eq) in DCM (800 mL) is added TEA (16.6 g, 164 mmol, 22.8 mL, 4.00 eq) dropwise at 0 °C, the mixture is stirred at 15 °C for 16 hrs. LCMS (EW33072-12-P1B, Rt = 0.844 min) showed the desired mass is detected. The reaction mixture is diluted with DCM (400 mL) and washed with aq. NaHCO₃ (400 mL * 1) and brine (400 mL * 1), then the mixture is diluted with DCM (2.00 L) and washed with 0.7 M Na₂CO₃ (1000 mL * 3) and brine (800 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is used to next step directly without purification. Compound **6** (80.0 g, crude) is obtained as white solid and confirmed via ¹H NMR: EW33072-12-P1A, 400 MHz, MeOD δ 7.02 - 7.04 (m, 2 H), 6.68 - 6.70 (m, 2 H), 5.34 - 5.35 (s, 3 H), 5.07 - 5.08 (d, *J* = 4.00 Hz, 3 H), 4.62 - 4.64 (d, *J* = 8.00 Hz, 3 H), 3.71 - 4.16 (m, 16 H), 3.31 - 3.70 (m, 44 H), 2.80 - 2.83 (m, 2 H), 2.68 (m, 2 H), 2.46 - 2.47 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.94 - 1.95 (d, *J* = 4.00 Hz, 18 H).

General procedure for preparation of TriGNal-TRIS-Peg2-Phosph 8c

[00266] Two batches are synthesized in parallel. To a solution of compound **6C** (40.0 g, 21.1 mmol, 1.00 eq) in DCM (600 mL) is added diisopropylammonium tetrazolide (3.62 g, 21.1 mmol, 1.00 eq) and compound **7c** (6.37 g, 21.1 mmol, 6.71 mL, 1.00 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 1 hr, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 30 mins, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 1.5 hrs. LCMS (EW33072-17-P1C1, Rt = 0.921 min) showed the desired MS+1 is detected. LCMS (EW33072-17-P1C2, Rt = 0.919 min) showed the desired MS+1 is detected. Two batches are combined for work-up. The mixture is

diluted with DCM (1.20 L), washed with saturated NaHCO₃ aqueous solution (1.60 L * 2), 3% DMF in H₂O (1.60 L * 2), H₂O (1.60 L * 3), brine (1.60 L), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is purified by column chromatography (SiO₂, DCM: MeOH: TEA = 100: 3: 2) TLC (SiO₂, DCM: MeOH = 10:1, R_f = 0.45), then concentrated under reduced pressure to give a residue. **Compound 8C** (76.0 g, 34.8 mmol, 82.5% yield, 96.0% purity) is obtained as white solid and confirmed via ¹HNMR: EW33072-19-P1C, 400 MHz, MeOD

δ 7.13-7.15 (d, J = 8.50 Hz, 2 H), 6.95-6.97 (dd, J = 8.38, 1.13 Hz, 2 H), 5.34 (d, J = 2.88 Hz, 3 H), .09 (dd, J = 11.26, 3.38 Hz, 3 H), 4.64 (d, J = 8.50 Hz, 3 H), 3.99 - 4.20 (m, 12 H), 3.88 - 3.98 (m, 5 H), 3.66 - 3.83 (m, 20 H), 3.51 - 3.65 (m, 17 H), 3.33 - 3.50 (m, 9 H), 2.87 (t, J = 7.63 Hz, 2 H), 2.76 (t, J = 5.94 Hz, 2 H), 2.42 - 2.50 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.94 - 1.95 (d, J = 6.13 Hz, 18 H), 1.24-1.26 (d, J = 6.75 Hz, 6 H), 1.18-1.20 (d, J = 6.75 Hz, 6 H)

Example 12: Modification motif 1

[00267] An example MSTIR siRNA includes a combination of the following modifications:

- Position 9 (from 5' to 3') of the sense strand is 2' F.
- If position 9 is a pyrimidine then all purines in the Sense Strand are 2' OMe, and 1-5 pyrimidines between positions 5 and 11 are 2' F provided that there are never three 2' F modifications in a row.
- If position 9 is a purine then all pyrimidines in the Sense Strand are 2' OMe, and 1-5 purines between positions 5 and 11 are 2' F provided that there are never three 2' F modifications in a row.
- Antisense strand odd-numbered positions are 2' OMe and even-numbered positions are a mixture of 2' F, 2' OMe and 2' deoxy.

Example 13: Modification motif 2

[00268] An example MSTIR siRNA includes a combination of the following modifications:

- Position 9 (from 5' to 3') of the sense strand is 2' deoxy.
- Sense strand positions 5, 7 and 8 are 2' F.
- All pyrimidines in positions 10-21 are 2' OMe, and purines are a mixture of 2' OMe and 2' F. Alternatively, all purines in positions 10-21 are 2' OMe and all pyrimidines in positions 10-21 are a mixture of 2' OMe and 2' F.
- Antisense strand odd-numbered positions are 2' OMe and even-numbered positions are a mixture of 2' F, 2' OMe and 2' deoxy.

[00269] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and compositions within the scope of these claims and their equivalents be covered thereby.

IV. SEQUENCE INFORMATION

[00270] Some embodiments include one or more nucleic acid sequences as described in **Table 13**:

Table 13. Sequence Information

SEQ ID NO:	Description
1-4754	MST1R siRNA sense strand sequences
4755-9508	MST1R siRNA antisense strand sequences
9509-9611	Base sequences of modified MST1R siRNA sense strand sequences
9612-9714	Base sequences of modified MST1R siRNA antisense strand sequences
9715-9817	Base sequences of alternatively modified MST1R siRNA sense strand sequences
9818	Full-length human <i>MST1R</i> mRNA sequence (Ensembl transcript ID: ENST00000296474.8) (human RNA)
9819-9836	Modification patterns 1S to 9S, 1AS to 8AS, and ASO1
9837-9839	Examples of RGD peptide sequences

CLAIMS

What is claimed is:

1. A composition comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount increases a lung function 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 lung function measurement is increased by about 10% or more, as compared to prior to administration.
4. A composition comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases a leukocyte measurement.
5. The composition of claim 4, wherein the leukocyte measurement comprises a lung leukocyte measurement.
6. The composition of claim 4, wherein the leukocyte measurement comprises a circulating leukocyte measurement.
7. The composition of claim 4, wherein the leukocyte measurement comprises a neutrophil measurement, eosinophil measurement, basophil measurement, monocyte measurement, or lymphocyte measurement, or a combination thereof.
8. The composition of claim 4, wherein the leukocyte measurement is decreased by about 10% or more, as compared to prior to administration.
9. A composition comprising an oligonucleotide that targets *MST1R* and when administered to a subject in an effective amount decreases a chronic obstructive pulmonary disease (COPD) or asthma exacerbation measurement.
10. The composition of claim 9, wherein the COPD or asthma exacerbation measurement is decreased by about 10% or more, as compared to prior to administration.
11. The composition of any one of claims 1, 4 or 9, wherein the oligonucleotide comprises a modified internucleoside linkage.
12. The composition of claim 11, wherein the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof.
13. The composition of claim 11, wherein the modified internucleoside linkage comprises one or more phosphorothioate linkages.
14. The composition of any one of claims 1, 4 or 9, 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.
15. The composition of any one of claims 1, 4 or 9, wherein the oligonucleotide comprises a modified nucleoside.

16. The composition of claim 15, wherein the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof.
17. The composition of claim 15, wherein the modified nucleoside comprises a LNA.
18. The composition of claim 15, wherein the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid.
19. The composition of claim 15, wherein the modified nucleoside comprises a 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.
20. The composition of claim 15, wherein the modified nucleoside comprises one or more 2' fluoro modified nucleosides.
21. The composition of claim 15, wherein the modified nucleoside comprises a 2' O-alkyl modified nucleoside.
22. The composition of any one of claims 1, 4 or 9, 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.
23. The composition of any one of claims 1, 4 or 9, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide.
24. The composition of claim 23, wherein the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α -tocopherol, or a combination thereof.
25. The composition of any one of claims 1, 4 or 9, wherein the oligonucleotide comprises an integrin targeting ligand attached at a 3' or 5' terminus of the oligonucleotide.
26. The composition of claim 25, wherein the integrin comprises integrin α -v- β -6.
27. The composition of claim 25, wherein the integrin targeting ligand comprises an arginine-glycine-aspartic acid (RGD) peptide.
28. The composition of any one of claims 1, 4 or 9, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand.
29. The composition of claim 28, wherein the sense strand is 12-30 nucleosides in length.
30. The composition of claim 28, wherein the antisense strand is 12-30 nucleosides in length.
31. A composition comprising an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 9818.
32. The composition of any one of claims 1, 4, 9 or 31, 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' methyl modified pyrimidines;

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

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

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

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

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

33. The composition of any one of claims 1, 4, 9 or 31, 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' methyl modified pyrimidines;

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

all purines comprise 2' 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' methyl modified purines;

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

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

34. The composition of any one of claims 1, 4 or 9, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO).

35. The composition of claim 34, wherein the ASO is 12-30 nucleosides in length.

36. A composition comprising an oligonucleotide that inhibits the expression of *MST1R*, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and a nucleoside sequence complementary to about 12-30 contiguous nucleosides of SEQ ID NO: 9818.

37. The composition of any one of claims 1, 4, 9, 31 or 36, further comprising a pharmaceutically acceptable carrier.

38. A method of treating a subject having a lung disorder, comprising administering an effective amount of the composition of claim 37 to the subject.

39. The method of claim 38, wherein the lung disorder comprises COPD, acute exacerbation of COPD, emphysema, chronic bronchitis, asthma, status asthmaticus, asthma-COPD overlap syndrome (ACOS), cough, lung cancer, interstitial lung disease, or pulmonary fibrosis.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/33350

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61P 35/00; ADD. C07K 14/47 (2022.01)

CPC - INV. C12N 15/113; ADD. C12Q 1/6886, G01N 33/6893, C12N 2310/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2010/0061977 A1 (RUBEN et al.) 11 March 2010 (11.03.2010) Claim 4; para [0123]; para [0125]; para [0339]; para [0343]; para [0391]; para [0468]; para [0654]; para [0785]	31, 37/31 ----- 1-3, 28-30, 37/1
Y	WANG et al., Roles of macrophage stimulating protein and tyrosine kinase receptor RON in smoke-induced airway inflammation of rats. Int J Clin Exp Pathol, 2015; Vol. 8, No.8, p8797-8808. Abstract	1, 3, 28-30, 37/1
Y	US 2013/0303932 A1 (HELFENBEIN et al.) 14 November 2013 (14.11.2013) Abstract; para [0002]; para [0031]	2

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 September 2022

Date of mailing of the international search report

NOV 07 2022

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Kari Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/33350

Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/33350

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

---Please see continuation in first extra sheet -----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, (28-31, 37) (in part), limited to siRNA with antisense strand comprising 12-30 contiguous nucleosides of SEQ ID NO:9818, to increase lung function measurement

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/33350

Continuation of Box No. III. Observations where unity of invention is lacking.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+, Claims 1-37, directed to a composition comprising an oligonucleotide that targets MST1R. The composition will be searched to the extent that the composition encompasses an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO:9818, further wherein the composition when administered to a subject in an effective amount increases a lung function measurement (note, these are the first claimed sequences for the inventive composition). The first named invention was determined based on the combination of first claimed unmodified oligonucleotide agent (siRNA) and sequence (claim 31) and phenotype (claim 1) for the inventive composition embodiment. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. It is believed that claims 1-3, (28-31, 37) (in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that the composition encompasses an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO:9818, further wherein the composition when administered to a subject in an effective amount increases a lung function measurement.

Additional composition(s) comprising additional oligonucleotide agent(s) with additional sequence(s), modification(s) (e.g., modified internucleoside linkage(s), nucleoside(s), lipid(s), targeting moieties, and/or modified purines/pyrimidines, will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected composition(s) comprising additional oligonucleotide agent(s) with additional sequence(s), modification(s) (e.g., modified internucleoside linkage(s), nucleoside(s), lipid(s), targeting moieties, and/or modified purines/pyrimidines. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a composition comprising a siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO:9818, further wherein the composition when administered to a subject in an effective amount decreases a leukocyte measurement (claims 4-8, (28-31, 37) (in part)).

Group II, claims 38-39, directed to a method of treating a subject having a lung disorder.

The inventions listed as Groups I+ and II do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

Group I+ has the special technical feature of a composition comprising an oligonucleotide that targets MST1R, that is not required by Group II.

Group II has the special technical feature of a method of treating a subject having a lung disorder, that is not required by Group I+.

Common technical features

Groups I+ and II share the technical features of including:
treating a subject having a lung disorder, comprising administering an effective amount of a composition comprising an oligonucleotide that targets MST1R to the subject.

However, these shared technical features are previously disclosed by prior art, as discussed below.

Group I+ inventions additionally share the technical features of including:
a composition comprising an oligonucleotide that targets MST1R and when administered to a subject in an effective amount increases a lung function measurement, decreases a leukocyte measurement, or decreases a chronic obstructive pulmonary disease (COPD) or asthma exacerbation measurement, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and a nucleoside sequence or an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length.

However, these shared technical features are made obvious by US 2016/0367534 A1 to University of Utah Research Foundation (hereinafter 'Univ Utah') in view of the article entitled "Roles of macrophage stimulating protein and tyrosine kinase receptor RON in smoke-induced airway inflammation of rats" by Wang et al., (Int J Clin Exp Pathol 2015; Vol. 8, No.8, p8797-8808) (hereinafter 'Wang').

-----please see continuation on next sheet -----

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/33350

Continuation of Box No. III. Observations where unity of invention is lacking.

Univ Utah teaches treatment of bone disease by administering to the subject an inhibitor of RON comprising a siRNA (Claim 1 - 'A method for inhibiting osteolysis or treating osteoporosis in a subject in need thereof, the method comprising administering to the subject an effective amount of at least one RON inhibitor.'; para [0044] - 'Provided herein are RON inhibitors and compositions comprising the same. RON inhibitors encompass agents that inhibit the activity of RON under physiological conditions. ... An inhibitor may prevent or reduce expression of the protein. For example, a therapeutic composition adapted to reduce the amount or the activity of the protein may comprise a small molecule inhibitor of the protein itself or of a binding partner, an antibody specific for the protein, or a siRNA. In some embodiments, the therapeutic composition may comprise a siRNA adapted to reduce the expression of the protein.'; Note, RON is also known as MSP1R). Univ Utah does not expressly teach siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length. However, since siRNA design was well known in the art, it would have been obvious to one of ordinary skill in the art that the siRNA targeting RON could comprise a sense strand and an antisense strand, wherein each strand is independently about 12-30 nucleosides in length, according to well known concepts in siRNA design. Univ Utah fails to teach an effective amount of siRNA increases a lung function measurement, decreases a leukocyte measurement, or decreases a chronic obstructive pulmonary disease (COPD) or asthma exacerbation measurement.

Wang teaches MSP and its receptor RON are involved in the smoke-induced airway inflammation (Abstract - 'When compared with healthy rats, MSP increased in the serum and bronchoalveolar lavage fluid (BALF) of smoking rats in a time dependent manner. In smoking rats, the RON expression in the lung and AM was higher than in healthy rats, and these increases were time dependent. MSP stimulated the production of malondialdehyde (MDA) and reduced superoxide dismutase (SOD) activity in rat AM cells in a dose dependent manner. MSP also stimulated the release of inflammatory factors TNF- α , IL-8, IL-1 β and IL-10 in rat AM in a dose-dependent manner. Moreover, at the same MSP concentration, the contents of MDA, TNF- α , IL-8 and IL-1 β in the AM of smoking rates were higher than in healthy rats, while the IL-10 content and SOD activity were lower than in healthy rats. Conclusion: MSP and its receptor RON are involved in the smoke-induced airway inflammation in rats via promoting AM to release inflammatory cytokines and inducing the increase of oxygen free radical.'). It would have been obvious to one of ordinary skill in the art that treatment with MSP1R siRNA of Univ Utah could be used to inhibit smoke-induced airway inflammation according to Wang, thereby promoting lung function measurement.

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I+ and II inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.