

RNAi Agents for Inhibiting Expression of Mucin 5AC (MUC5AC), Compositions Thereof, and Methods of Use

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from United States Provisional Patent Application Serial No. 63/194,370, filed on May 28, 2021, the contents of which are incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] This application contains a Sequence Listing which has been submitted in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy is named SEQLIST_30659.txt and is 460 kb in size.

FIELD OF THE INVENTION

[0003] The present disclosure relates to RNA interference (RNAi) agents, e.g., double stranded RNAi agents, for inhibition of Mucin 5AC ("MUC5AC") gene expression, compositions that include MUC5AC RNAi agents, and methods of use thereof.

BACKGROUND

[0004] MUC5AC is a transcriptionally regulated secreted mucin expressed in airway epithelia of the lung and in other mucosal tissues (for example, gastrointestinal, urogenital, eye, and ear) (Lillehoj et al, Int Rev Cell Mol Biol, 2013). In airways, MUC5AC and MUC5B are the major gel-forming mucins. MUC5B is constitutively expressed and is required for mucociliary clearance (Roy et al., Nature 2014). Normal subjects have a relatively higher expression of MUC5B versus MUC5AC in the trachea and proximal airways, with this ratio further increasing in distal airways with expression of MUC5AC almost undetectable in distal and terminal bronchioles (Okuda et al., AJRCCM 2019). Typically expressed at low levels in the airway, MUC5AC expression can be robustly induced by external stress stimuli like pro-inflammatory mediators (including, for example, type 2 cytokines: IL-4, IL-9, IL-17, IL-23 and IL-13), noxious inhaled substances (for example, cigarette smoke, acrolein, toxic gases), viral infections, and allergens. The resulting mucus hypersecretion and hyperconcentration is understood to be a common

pathogenic mechanism linked to airway obstruction in severe asthma and other mucoobstructive lung diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), non-CF bronchiectasis (NCFB), and primary ciliary dyskinesia (PCD) (Boucher, NEJM 2019). In asthma, COPD, and NCFB patients, exaggerated expression and secretion of MUC5AC results in a narrowing of airway lumen, airway obstruction, and exacerbations (Dunican et al., JCI 2017; Bonser et al., JCI 2016; Kesimer et al., NEJM 2017; Ramsey et al., AJRCCM 2019). A genome-wide association study (GWAS) identified a novel MUC5AC allele linked to increased MUC5AC expression and patients with moderate-to-severe asthma (Shrine et al., Lancet Respir Med 2019). Experimental evidence from MUC5AC-deficient mice demonstrated that MUC5AC-mediated airway plugging is a major contributor to airway hyperresponsiveness to allergens independent of inflammation and bronchoconstriction (Evans et al, Nat Commun, 2015). Current standard of care treatments for severe asthma and other mucoobstructive lung diseases include bronchodilators and anti-inflammatory therapeutics (such as corticosteroids and biologics), but currently available treatments do not directly address pathogenic mucin overexpression and hypersecretion. Alternative approaches that directly treat mucus hypersecretion and obstruction are needed.

[0005] Increased expression of MUC5AC has also been observed in malignancies such as lung adenocarcinomas, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, ovarian cancer, and other tumors (Krishn et al., Carcinogenesis 2018), where it has been linked to migration and invasiveness of tumor cells. Loss-of-function mutations in MUC5AC and other mucin genes are significantly underrepresented in tumor cells, suggesting that mucin overexpression may shield tumors from recognition by immune cells (Gorlov et al., Cancer Genetics 2019). Tumor MUC5AC overexpression is associated with progression and poor survival in lung adenocarcinoma patients (Bauer et al., JCI Insight 2018). MUC5AC overexpression has also been linked to number of other conditions including: allergic rhinitis, chronic rhinosinusitis, otitis media, Barret's esophagus, pancreatitis, and inflammatory bowel disease (Krishn et al., Carcinogenesis 2018).

SUMMARY

[0006] There exists a need for novel RNA interference (RNAi) agents (termed RNAi agents, RNAi triggers, or triggers), *e.g.*, double stranded RNAi agents, that are able to selectively and efficiently inhibit the expression of a MUC5AC gene, including for use as a therapeutic

or medicament. Further, there exists a need for compositions of novel MUC5AC-specific RNAi agents for the treatment of diseases or disorders associated with mucus hypersecretion and obstruction (referred to herein as “mucoobstructive” lung diseases and disorders) such as for example cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), non-CF bronchiectasis (NCFB), primary ciliary dyskinesia (PCD), and asthma, and/or diseases or disorders that can be mediated at least in part by a reduction in MUC5AC gene expression and/or MUC5AC protein levels.

[0007] The nucleotide sequences and chemical modifications of the MUC5AC RNAi agents disclosed herein, as well as their combination with certain specific targeting ligands suitable for selectively and efficiently delivering the MUC5AC RNAi agents *in vivo*, differ from what is known in the art. The MUC5AC RNAi agents disclosed herein provide for highly potent and efficient inhibition of the expression of a MUC5AC gene and have sequences suitable for use as a therapeutic for the treatment of diseases and disorders.

[0008] In general, the present disclosure features MUC5AC gene-specific RNAi agents, compositions that include MUC5AC RNAi agents, and methods for inhibiting expression of a MUC5AC gene *in vitro* and/or *in vivo* using the MUC5AC RNAi agents and compositions that include MUC5AC RNAi agents described herein. The MUC5AC RNAi agents described herein are able to selectively and efficiently decrease expression of a MUC5AC gene, and thereby reduce the expression of the MUC5AC protein, which can lead to a therapeutic benefit such as, for example, a reduction in mucoobstruction in the lung.

[0009] The described MUC5AC RNAi agents can be used in methods for therapeutic treatment (including preventative or prophylactic treatment) of symptoms and diseases including, but not limited to, mucoobstructive lung diseases (such as asthma, CF, COPD, NCFB, PCD), allergic bronchopulmonary aspergillosis, interstitial lung diseases, cancer (such as lung adenocarcinomas, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, ovarian cancer, and other tumors), respiratory infections (such as respiratory syncytial virus, influenza, rhinovirus), otitis media, inflammatory bowel disease, gallstone disease, allergic rhinitis, chronic rhinosinusitis and nasal polypsis.

[0010] In one aspect, the disclosure features RNAi agents for inhibiting expression of a MUC5AC gene, wherein the RNAi agent includes a sense strand (also referred to as a passenger strand) and an antisense strand (also referred to as a guide strand). The sense strand and the antisense strand can be partially, substantially, or fully complementary to each other. The length of the RNAi agent sense strands described herein each can be 15 to

49 nucleotides in length. The length of the RNAi agent antisense strands described herein each can be 18 to 49 nucleotides in length. In some embodiments, the sense and antisense strands are independently 18 to 26 nucleotides in length. The sense and antisense strands can be either the same length or different lengths. In some embodiments, the sense and antisense strands are independently 21 to 26 nucleotides in length. In some embodiments, the sense and antisense strands are independently 21 to 24 nucleotides in length. In some embodiments, both the sense strand and the antisense strand are 21 nucleotides in length. In some embodiments, the antisense strands are independently 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the sense strands are independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 nucleotides in length. The RNAi agents described herein, upon delivery to a cell expressing MUC5AC, inhibit the expression of one or more MUC5AC gene variants *in vivo* and/or *in vitro*.

[0011] The MUC5AC RNAi agents disclosed herein target a human MUC5AC gene (*see, e.g.,* SEQ ID NO:1). In some embodiments, the MUC5AC RNAi agents disclosed herein target a portion of a MUC5AC gene having the sequence of any of the sequences disclosed in Table 1.

[0012] In another aspect, the disclosure features compositions, including pharmaceutical compositions, that include one or more of the disclosed MUC5AC RNAi agents that are able to selectively and efficiently decrease expression of a MUC5AC gene. The compositions that include one or more MUC5AC RNAi agents described herein can be administered to a subject, such as a human or animal subject, for the treatment (including prophylactic treatment or inhibition) of symptoms and diseases associated with MUC5AC gene expression and/or MUC5AC protein levels.

[0013] Examples of MUC5AC RNAi agent sense strands and antisense strands that can be used in a MUC5AC RNAi agent are provided in Tables 3, 4, 5, 6, and 7. Examples of MUC5AC RNAi agent duplexes are provided in Tables 8A, 8B, 8C, 9, 10A, 10B, and 11. Examples of 19-nucleotide core stretch sequences that may consist of or may be included in the sense strands and antisense strands of certain MUC5AC RNAi agents disclosed herein, are provided in Table 2.

[0014] In another aspect, the disclosure features methods for delivering MUC5AC RNAi agents to epithelial cells in a subject, such as a mammal, *in vivo*. Also described herein are compositions for use in such methods. In some embodiments, disclosed herein are methods

for delivering MUC5AC RNAi agents to pulmonary cells (epithelial cells, macrophages, smooth muscle, endothelial cells) to a subject *in vivo*. In some embodiments, the subject is a human subject.

[0015] The methods disclosed herein include the administration of one or more MUC5AC RNAi agents to a subject, e.g., a human or animal subject, by any suitable means known in the art. The pharmaceutical compositions disclosed herein that include one or more MUC5AC RNAi agents can be administered in a number of ways depending upon whether local or systemic treatment is desired. Administration can be, but is not limited to, for example, intravenous, intraarterial, subcutaneous, intraperitoneal, subdermal (e.g., via an implanted device), and intraparenchymal administration. In some embodiments, the pharmaceutical compositions described herein are administered by inhalation (such as dry powder inhalation or aerosol inhalation), intranasal administration, intratracheal administration, or oropharyngeal aspiration administration.

[0016] In some embodiments, it is desired that the MUC5AC RNAi agents described herein inhibit the expression of an MUC5AC gene in the pulmonary epithelium, for which the administration is by inhalation (e.g., by an inhaler device, such as a metered-dose inhaler, or a nebulizer such as a jet or vibrating mesh nebulizer, or a soft mist inhaler).

[0017] The one or more MUC5AC RNAi agents can be delivered to target cells or tissues using any oligonucleotide delivery technology known in the art. In some embodiments, a MUC5AC RNAi agent is delivered to cells or tissues by covalently linking the RNAi agent to a targeting group. In some embodiments, the targeting group can include a cell receptor ligand, such as an integrin targeting ligand. Integrins are a family of transmembrane receptors that facilitate cell-extracellular matrix (ECM) adhesion. In particular, integrin α -v-beta-6 (α v β 6) is an epithelial-specific integrin that is known to be a receptor for ECM proteins and the TGF-beta latency-associated peptide (LAP), and is expressed in various cells and tissues. Integrin α v β 6 is known to be highly upregulated in injured pulmonary epithelium. In some embodiments, the MUC5AC RNAi agents described herein are linked to an integrin targeting ligand that has affinity for integrin α v β 6. As referred to herein, an " α v β 6 integrin targeting ligand" is a compound that has affinity for integrin α v β 6, which can be utilized as a ligand to facilitate the targeting and delivery of an RNAi agent to which it is attached to the desired cells and/or tissues (i.e., to cells expressing integrin α v β 6). In some embodiments, multiple α v β 6 integrin targeting ligands or clusters of α v β 6 integrin targeting ligands are linked to a MUC5AC RNAi agent. In some embodiments, the

MUC5AC RNAi agent- $\alpha\beta6$ integrin targeting ligand conjugates are selectively internalized by lung epithelial cells, either through receptor-mediated endocytosis or by other means.

[0018] Examples of targeting groups useful for delivering MUC5AC RNAi agents that include $\alpha\beta6$ integrin targeting ligands are disclosed, for example, in International Patent Application Publication No. WO 2018/085415 and International Patent Application Publication No. WO 2019/089765, the contents of each of which are incorporated by reference herein in their entirety.

[0019] A targeting group can be linked to the 3' or 5' end of a sense strand or an antisense strand of a MUC5AC RNAi agent. In some embodiments, a targeting group is linked to the 3' or 5' end of the sense strand. In some embodiments, a targeting group is linked to the 5' end of the sense strand. In some embodiments, a targeting group is linked internally to a nucleotide on the sense strand and/or the antisense strand of the RNAi agent. In some embodiments, a targeting group is linked to the RNAi agent via a linker.

[0020] In another aspect, the disclosure features compositions that include one or more MUC5AC RNAi agents that have the duplex structures disclosed in Tables 8A, 8B, 8C, 9, 10A, 10B, and 11.

[0021] The use of MUC5AC RNAi agents provides methods for therapeutic (including prophylactic) treatment of diseases or disorders for which a reduction in MUC5AC gene expression and/or a reduction in MUC5AC protein levels can provide a therapeutic benefit. The MUC5AC RNAi agents disclosed herein can be used to treat various diseases, including mucoobstructive lung diseases (such as asthma, CF, COPD, NCFB, PCD), allergic bronchopulmonary aspergillosis, interstitial lung diseases, cancer (such as lung adenocarcinomas, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, ovarian cancer, and other tumors), respiratory infections (such as respiratory syncytial virus, influenza, rhinovirus), otitis media, inflammatory bowel disease, gallstone disease, allergic rhinitis, chronic rhinosinusitis and nasal polyposis. In some embodiments, the MUC5AC RNAi agents disclosed herein can be used to treat a mucoobstructive lung disease, such as severe asthma or COPD. MUC5AC RNAi agents can further be used to treat, for example, various cancers. Such methods of treatment include administration of a MUC5AC RNAi agent to a human being or animal having elevated or enhanced MUC5AC gene expression and/or MUC5AC protein levels above what is desired.

[0022] One aspect described herein is an RNAi agent for inhibiting expression of a MUC5AC gene, comprising:

- (i) an antisense strand that is between 18 and 49 nucleotides in length that includes a nucleotide sequence at least partially complementary to a corresponding stretch of contiguous nucleotides of the MUC5AC gene transcript (SEQ ID NO:1); and
- (ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand;

wherein the RNAi agent sense strand is optionally further linked to a targeting ligand, and wherein RNAi agent is capable of inhibiting expression of a MUC5AC gene.

[0023] Another aspect described herein is an RNAi agent for inhibiting expression of a MUC5AC gene, comprising:

- (i) an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 3; and
- (ii) a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand;

wherein the RNAi agent sense strand is optionally further linked to a targeting ligand, and wherein RNAi agent is capable of inhibiting expression of a MUC5AC gene.

[0024] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5' → 3') UUGUAGUAGUCGCAGAACAGC (SEQ ID NO: 1525). In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5' → 3') UUGUAGUAGUCGCAGAACAGC (SEQ ID NO: 1525), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5' → 3') UUGUAGUAGUCGCAGAACAGC (SEQ ID NO: 1525), wherein SEQ ID NO: 1525 is located at positions 1-21 (5' → 3') of the antisense strand.

[0025] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide

sequence differing by no more than 1 nucleotide from the nucleotide sequence (5' → 3') cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO: 1127), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 3A through 3J showing all internucleoside linkages). In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5' → 3') cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO: 1127), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0026] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5' → 3') usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO: 1065), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5' → 3') usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO: 1065), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0027] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5' → 3') UUCUUGUUCAGGCAAAUCAGC (SEQ ID NO: 1535). In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5' → 3') UUCUUGUUCAGGCAAAUCAGC (SEQ ID NO: 1535), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5' → 3') UUCUUGUUCAGGCAAAUCAGC (SEQ ID NO: 1535), wherein SEQ ID NO: 1535 is located at positions 1-21 (5' → 3') of the antisense strand.

[0028] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5' → 3') usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO: 1166), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 3A through 3J showing all internucleoside linkages). In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5' → 3') usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO: 1166), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0029] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide

sequence differing by no more than 1 nucleotide from the nucleotide sequence (5' → 3') cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO: 1191), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 3A through 3J showing all internucleoside linkages). In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5' → 3') cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO: 1191), wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

[0030] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525); or

UUCUUGUUCAGGCAAAUCAGC (SEQ ID NO:1535);

wherein the MUC5AC RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; and wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides.

[0031] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525); or

UUCUUGUUCAGGCAAAUCAGC (SEQ ID NO:1535);

wherein the MUC5AC RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides

on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound having affinity for an integrin receptor.

[0032] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525); or

UUCUUGUUCAGGCAAUCAGC (SEQ ID NO:1535);

wherein the MUC5AC RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound having affinity for an integrin receptor; and wherein the respective antisense strand sequence is located at positions 1-21 of the antisense strand.

[0033] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand and a sense strand, wherein the antisense strand and the sense strand consist of, consist essentially of, or comprise nucleotide sequences that differ by 0 or 1 nucleotides from one of the following nucleotide sequence (5' → 3') pairs:

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525) and

GCUGUUCUGCGACUACUACAA (SEQ ID NO: 1617); or

UUCUUGUUCAGGCAAUCAGC (SEQ ID NO:1535) and

GCUGAUUUGCCUGAACAAAGAA (SEQ ID NO: 1632); or

wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides.

[0034] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand and a sense strand, wherein the antisense strand and the sense strand consist of, consist essentially of, or comprise nucleotide sequences that differ by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3') pairs:

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525) and

GCUGUUCUGCGACUACUACAA (SEQ ID NO: 1617); or
 UUCUUGUUCAGGCAAUCAGC (SEQ ID NO:1535) and
 GCUGAUUUGCCUGAACAAAGAA (SEQ ID NO: 1632); or

wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0035] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127);
 usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1065);
 usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166);
 cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191);

wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; s represents a phosphorothioate linkage; and wherein the MUC5AC RNAi agent further includes the sense strand that is at least partially complementary to the antisense strand; and wherein all or substantially all of the nucleotides of the sense strand are modified nucleotides.

[0036] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127);
 usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1065);
 usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166);
 cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191);

wherein the MUC5AC RNAi agent further includes the sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the

nucleotides of the sense strand are modified nucleotides; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 5' terminal end, wherein the targeting ligand includes a compound with affinity for an integrin receptor.

[0037] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand and a sense strand that consists of, consists essentially of, or comprises one of the following nucleotide sequence pairs (5' → 3'):

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127) and
 gscuguucuGfCfGfacuacuacaa (SEQ ID NO:1265);
 usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO: 1065) and
 gscuguucuGfCfGfacuacuacaa (SEQ ID NO:1265);
 usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166) and
 gscugauUfuGfcCfugaacaagaa (SEQ ID NO: 1315); and
 cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191) and
 gscugauUfuGfcCfugaacaagaa (SEQ ID NO: 1315); and

wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; and s represents a phosphorothioate linkage; and wherein the sense strand also includes a targeting ligand having affinity for an integrin receptor, wherein the targeting ligand is optionally linked at the 5'-end of the sense strand.

[0038] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand and a sense strand that consists of, consists essentially of, or comprises modified nucleotide sequences that differs by 0 or 1 nucleotides from one of the following sequence pairs (5' → 3'):

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127) and
 Tri-SM6.1-avb6-(TA14)gscuguucuGfCfGfacuacuacaas(invAb) (SEQ ID
 NO:1491);
 usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1065) and
 Tri-SM6.1-avb6-(TA14)gscuguucuGfCfGfacuacuacaas(invAb) (SEQ ID NO:
 1491);

usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166) and
 Tri-SM6.1-avb6-(TA14)gscugauUfuGfcCfugaacaagaas(invAb) (SEQ ID NO:
 1513);

cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191) and
 Tri-SM6.1-avb6-(TA14)gscugauUfuGfcCfugaacaagaas(invAb) (SEQ ID NO:
 1513);

wherein a, c, g, and u represent 2'-O-methyl adenosine, cytidine, guanosine, and uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro adenosine, cytidine, guanosine, and uridine, respectively; cPrpu represents a 5'-cyclopropyl phosphonate-2'-O-methyluridine; Tri-SM6.1- $\alpha\text{v}\beta\text{6}$ -(TA14) represents the tridentate $\alpha\text{v}\beta\text{6}$ epithelial cell targeting ligand with the chemical structure as shown in Fig. 1; (invAb) represents an inverted abasic deoxyribonucleotide (see also Table 11), and s represents a phosphorothioate linkage.

[0039] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5' $\rightarrow$ 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); and
 UUCUUGUUCAGGCAAUAUCA (SEQ ID NO:83).

[0040] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5' $\rightarrow$ 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); and
 UUCUUGUUCAGGCAAUAUCA (SEQ ID NO:83);

wherein all or substantially all of the nucleotides are modified nucleotides.

[0041] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5' $\rightarrow$ 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); and
 UUCUUGUUCAGGCAAUAUCA (SEQ ID NO:83);

wherein all or substantially all of the nucleotides are modified nucleotides, and wherein SEQ ID NO:79 and SEQ ID NO: 83, respectively, is located at nucleotide positions 1-19 (5' $\rightarrow$ 3') of the antisense strand.

[0042] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand and a sense strand that each include a nucleobase sequences that differs by

0 or 1 nucleobases from the nucleotide sequence pairs selected from the group consisting of (5' → 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); and
 UGUUCUGCGACUACUACAA (SEQ ID NO:568); or
 UUCUUGUUCAGGCAAUA (SEQ ID NO:83) and
 UGAUUUGCCUGAACAAGAA (SEQ ID NO:572).

[0043] In some embodiments, a MUC5AC RNAi agent disclosed herein includes an antisense strand and a sense strand that each include a nucleobase sequences that differs by 0 or 1 nucleobases from the nucleotide sequence pairs selected from the group consisting of (5' → 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); and
 UGUUCUGCGACUACUACAA (SEQ ID NO:568); or
 UUCUUGUUCAGGCAAUA (SEQ ID NO:83) and
 UGAUUUGCCUGAACAAGAA (SEQ ID NO:572); and

wherein all or substantially all of the nucleotides are modified nucleotides.

Definitions

[0044] As used herein, the terms “oligonucleotide” and “polynucleotide” mean a polymer of linked nucleosides each of which can be independently modified or unmodified.

[0045] As used herein, an “RNAi agent” (also referred to as an “RNAi trigger”) means a composition that contains an RNA or RNA-like (e.g., chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting (e.g., degrades or inhibits under appropriate conditions) translation of targeted messenger RNA (mRNA) transcripts in a sequence specific manner. As used herein, RNAi agents may operate through the RNA interference mechanism (i.e., inducing RNA interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). While it is believed that RNAi agents, as that term is used herein, operate primarily through the RNA interference mechanism, the disclosed RNAi agents are not bound by or limited to any particular pathway or mechanism of action. RNAi agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to: small (or short) interfering RNAs (siRNAs), double stranded RNAs (dsRNA), micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the RNAi agents described

herein is at least partially complementary to the mRNA being targeted (i.e., MUC5AC mRNA). RNAi agents can include one or more modified nucleotides and/or one or more non-phosphodiester linkages.

[0046] As used herein, the terms “silence,” “reduce,” “inhibit,” “down-regulate,” or “knockdown” when referring to expression of a given gene, mean that the expression of the gene, as measured by the level of RNA transcribed from the gene or the level of polypeptide, protein, or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is treated with the RNAi agents described herein as compared to a second cell, group of cells, tissue, organ, or subject that has not or have not been so treated.

[0047] As used herein, the terms “sequence” and “nucleotide sequence” mean a succession or order of nucleobases or nucleotides, described with a succession of letters using standard nomenclature. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation.

[0048] As used herein, a “base,” “nucleotide base,” or “nucleobase,” is a heterocyclic pyrimidine or purine compound that is a component of a nucleotide, and includes the primary purine bases adenine and guanine, and the primary pyrimidine bases cytosine, thymine, and uracil. A nucleobase may further be modified to include, without limitation, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. (*See, e.g., Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008). The synthesis of such modified nucleobases (including phosphoramidite compounds that include modified nucleobases) is known in the art.

[0049] As used herein, the term “nucleotide” has the same meaning as commonly understood in the art. Thus, the term “nucleotide” as used herein, refers to a glycoside comprising a sugar moiety, a base moiety and a covalently linked group (linkage group), such as a phosphate or phosphorothioate internucleoside linkage group, and covers both naturally occurring nucleotides, such as DNA or RNA, and non-naturally occurring nucleotides comprising modified sugar and/or base moieties, which are also referred to as nucleotide analogs or modified nucleotides herein. A single nucleotide may be referred to here as a monomer or unit.

[0050] As used herein, and unless otherwise indicated, the term “complementary,” when used to describe a first nucleobase or nucleotide sequence (e.g., RNAi agent sense strand or

targeted mRNA) in relation to a second nucleobase or nucleotide sequence (e.g., RNAi agent antisense strand or a single-stranded antisense oligonucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize (form base pair hydrogen bonds under mammalian physiological conditions (or otherwise suitable *in vivo* or *in vitro* conditions)) and form a duplex or double helical structure under certain standard conditions with an oligonucleotide that includes the second nucleotide sequence. The person of ordinary skill in the art would be able to select the set of conditions most appropriate for a hybridization test. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification. For example, a and Af, as defined herein, are complementary to U (or T) and identical to A for the purposes of determining identity or complementarity.

[0051] As used herein, “perfectly complementary” or “fully complementary” means that in a hybridized pair of nucleobase or nucleotide sequence molecules, all (100%) of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

[0052] As used herein, “partially complementary” means that in a hybridized pair of nucleobase or nucleotide sequence molecules, at least 70%, but not all, of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

[0053] As used herein, “substantially complementary” means that in a hybridized pair of nucleobase or nucleotide sequence molecules, at least 85%, but not all, of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

[0054] As used herein, the terms “complementary,” “fully complementary,” “partially complementary,” and “substantially complementary” are used with respect to the nucleobase or nucleotide matching between the sense strand and the antisense strand of an RNAi agent, or between the antisense strand of an RNAi agent and a sequence of an MUC5AC mRNA.

[0055] As used herein, the term “substantially identical” or “substantial identity,” as applied to a nucleic acid sequence means the nucleotide sequence (or a portion of a nucleotide sequence) has at least about 85% sequence identity or more, e.g., at least 90%, at least 95%, or at least 99% identity, compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the same type of nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. The inventions disclosed herein encompass nucleotide sequences substantially identical to those disclosed herein.

[0056] As used herein, the terms “treat,” “treatment,” and the like, mean the methods or steps taken to provide relief from or alleviation of the number, severity, and/or frequency of one or more symptoms of a disease in a subject. As used herein, “treat” and “treatment” may include the prevention, management, prophylactic treatment, and/or inhibition or reduction of the number, severity, and/or frequency of one or more symptoms of a disease in a subject.

[0057] As used herein, the phrase “introducing into a cell,” when referring to an RNAi agent, means functionally delivering the RNAi agent into a cell. The phrase “functional delivery,” means delivering the RNAi agent to the cell in a manner that enables the RNAi agent to have the expected biological activity, e.g., sequence-specific inhibition of gene expression.

[0058] Unless stated otherwise, use of the symbol  as used herein means that any group or groups may be linked thereto that is in accordance with the scope of the inventions described herein.

[0059] As used herein, the term “isomers” refers to compounds that have identical molecular formulae, but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are non-superimposable mirror images are termed “enantiomers,” or sometimes optical isomers. A carbon atom bonded to four non-identical substituents is termed a “chiral center.”

[0060] As used herein, unless specifically identified in a structure as having a particular conformation, for each structure in which asymmetric centers are present and thus give rise to enantiomers, diastereomers, or other stereoisomeric configurations, each structure disclosed herein is intended to represent all such possible isomers, including their optically pure and racemic forms. For example, the structures disclosed herein are intended to cover mixtures of diastereomers as well as single stereoisomers.

[0061] As used in a claim herein, the phrase “consisting of” excludes any element, step, or ingredient not specified in the claim. When used in a claim herein, the phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention.

[0062] The person of ordinary skill in the art would readily understand and appreciate that the compounds and compositions disclosed herein may have certain atoms (e.g., N, O, or S atoms) in a protonated or deprotonated state, depending upon the environment in which the compound or composition is placed. Accordingly, as used herein, the structures disclosed herein envisage that certain functional groups, such as, for example, OH, SH, or NH, may be protonated or deprotonated. The disclosure herein is intended to cover the disclosed compounds and compositions regardless of their state of protonation based on the environment (such as pH), as would be readily understood by the person of ordinary skill in the art. Correspondingly, compounds described herein with labile protons or basic atoms should also be understood to represent salt forms of the corresponding compound. Compounds described herein may be in a free acid, free base, or salt form. Pharmaceutically acceptable salts of the compounds described herein should be understood to be within the scope of the invention.

[0063] As used herein, the term “linked” or “conjugated” when referring to the connection between two compounds or molecules means that two compounds or molecules are joined by a covalent bond. Unless stated, the terms “linked” and “conjugated” as used herein may refer to the connection between a first compound and a second compound either with or without any intervening atoms or groups of atoms.

[0064] As used herein, the term “including” is used to herein mean, and is used interchangeably with, the phrase “including but not limited to.” The term “or” is used herein to mean, and is used interchangeably with, the term “and/or,” unless the context clearly indicates otherwise.

[0065] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0066] Where a value is explicitly recited, it is to be understood that values which are about the same quantity or amount as the recited value are also within the scope of the disclosure. Where a combination is disclosed, each sub-combination of the elements of that combination is also specifically disclosed and is within the scope of the disclosure. Conversely, where different elements or groups of elements are individually disclosed, combinations thereof are also disclosed. Where any element of a disclosure is disclosed as having a plurality of alternatives, examples of that disclosure in which each alternative is excluded singly or in any combination with the other alternatives are also hereby disclosed; more than one element of a disclosure can have such exclusions, and all combinations of elements having such exclusions are hereby disclosed.

[0067] Other objects, features, aspects, and advantages of the invention will be apparent from the following detailed description, accompanying figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0068] **FIG. 1.** Chemical structure representation of the tridentate $\alpha\beta6$ epithelial cell targeting ligand referred to herein as Tri-SM6.1- $\alpha\beta6$ -(TA14).

[0069] **FIG. 2.** Chemical structure representation of the peptide $\alpha\beta6$ epithelial cell targeting ligand referred to herein as $\alpha\beta6$ -pep1.

The following abbreviations are used in Figures 3A to 3J: a, c, g, i, and u are 2'-O-methyl modified nucleotides; Af, Cf, Gf, and Uf are 2'-fluoro modified nucleotides; o is a phosphodiester linkage; s is a phosphorothioate linkage; invAb is an inverted abasic residue (*see, e.g.*, Table 11); cPrpu is a 5'-cyclopropyl phosphonate-2'-O-methyluridine modified nucleotide (*see, e.g.*, Table 11); Tri-SM6.1- $\alpha\beta6$ -(TA14) is the tridentate $\alpha\beta6$ epithelial cell targeting ligand having the structure shown in Fig. 1; and (TriAlk14) is the linking

group as shown in Table 11, which is suitable for subsequent coupling to targeting ligands (*See also*, Example 1 herein).

[0070] FIG. 3A. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent conjugate having the structure of AC000437 (*see, e.g.*, Tables 9, 10, and 11), having a tridentate $\alpha v\beta 6$ epithelial cell targeting ligand linked at the 5' end of the sense strand.

[0071] FIG. 3B. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent conjugate having the structure of AC000480 (*see, e.g.*, Tables 9, 10, and 11), having a tridentate $\alpha v\beta 6$ epithelial cell targeting ligand linked at the 5' end of the sense strand.

[0072] FIG. 3C. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent conjugate having the structure of AC000482 (*see, e.g.*, Tables 9, 10, and 11), having a tridentate $\alpha v\beta 6$ epithelial cell targeting ligand linked at the 5' end of the sense strand.

[0073] FIG. 3D. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent conjugate having the structure of AC001305 (*see, e.g.*, Tables 9, 10, and 11), having a tridentate $\alpha v\beta 6$ epithelial cell targeting ligand linked at the 5' end of the sense strand.

[0074] FIG. 3E. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent conjugate having the structure of AC001306 (*see, e.g.*, Tables 9, 10, and 11), having a tridentate $\alpha v\beta 6$ epithelial cell targeting ligand linked at the 5' end of the sense strand.

[0075] FIG. 3F. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent duplex having the structure of AD08089 (*see, e.g.*, Tables 8 and 10), having a (TriAlk14) linker at the 5' end of the sense strand.

[0076] FIG. 3G. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent duplex having the structure of AD08174 (*see, e.g.*, Tables 8 and 10), having a (TriAlk14) linker at the 5' end of the sense strand.

[0077] FIG. 3H. Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent duplex having the structure of AD08173 (*see, e.g.*, Tables 8 and 10), having a (TriAlk14) linker at the 5' end of the sense strand.

[0078] **FIG. 3I.** Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent duplex having the structure of AD09240 (*see, e.g.*, Tables 8 and 10), having a (TriAlk14) linker at the 5' end of the sense strand.

[0079] **FIG. 3J.** Schematic diagram of the modified sense and antisense strands of the MUC5AC RNAi agent duplex having the structure of AD09241 (*see, e.g.*, Tables 8 and 10), having a (TriAlk14) linker at the 5' end of the sense strand.

DETAILED DESCRIPTION

RNAi Agents

[0080] Described herein are RNAi agents for inhibiting expression of a MUC5AC gene (referred to herein as MUC5AC RNAi agents or MUC5AC RNAi triggers). Each MUC5AC RNAi agent disclosed herein comprises a sense strand and an antisense strand. The sense strand can be 15 to 49 nucleotides in length. The antisense strand can be 18 to 49 nucleotides in length. The sense and antisense strands can be either the same length or they can be different lengths. In some embodiments, the sense and antisense strands are each independently 18 to 27 nucleotides in length. In some embodiments, both the sense and antisense strands are each 21-26 nucleotides in length. In some embodiments, the sense and antisense strands are each 21-24 nucleotides in length. In some embodiments, the sense and antisense strands are each independently 19-21 nucleotides in length. In some embodiments, the sense strand is about 19 nucleotides in length while the antisense strand is about 21 nucleotides in length. In some embodiments, the sense strand is about 21 nucleotides in length while the antisense strand is about 23 nucleotides in length. In some embodiments, a sense strand is 23 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, both the sense and antisense strands are each 21 nucleotides in length. In some embodiments, the RNAi agent antisense strands are each independently 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the RNAi agent sense strands are each independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 nucleotides in length. The sense and antisense strands are annealed to form a duplex, and in some embodiments, a double-stranded RNAi agent has a duplex length of about 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 nucleotides.

[0081] Examples of nucleotide sequences used in forming MUC5AC RNAi agents are provided in Tables 2, 3, 4, 5, 6, 7, and 11. Examples of RNAi agent duplexes, that include

the sense strand and antisense strand sequences in Tables 2, 3, 4, 5, 6, and 7 are shown in Tables 8A, 8B, 8C, 9, 10A, 10B, and 11.

[0082] In some embodiments, the region of perfect, substantial, or partial complementarity between the sense strand and the antisense strand is 15-26 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides in length and occurs at or near the 5' end of the antisense strand (e.g., this region may be separated from the 5' end of the antisense strand by 0, 1, 2, 3, or 4 nucleotides that are not perfectly, substantially, or partially complementary).

[0083] A sense strand of the MUC5AC RNAi agents described herein includes at least 15 consecutive nucleotides that have at least 85% identity to a core stretch sequence (also referred to herein as a "core stretch" or "core sequence") of the same number of nucleotides in an MUC5AC mRNA. In some embodiments, a sense strand core stretch sequence is 100% (perfectly) complementary or at least about 85% (substantially) complementary to a core stretch sequence in the antisense strand, and thus the sense strand core stretch sequence is typically perfectly identical or at least about 85% identical to a nucleotide sequence of the same length (sometimes referred to, *e.g.*, as a target sequence) present in the MUC5AC mRNA target. In some embodiments, this sense strand core stretch is 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In some embodiments, this sense strand core stretch is 17 nucleotides in length. In some embodiments, this sense strand core stretch is 19 nucleotides in length.

[0084] An antisense strand of a MUC5AC RNAi agent described herein includes at least 18 consecutive nucleotides that have at least 85% complementarity to a core stretch of the same number of nucleotides in an MUC5AC mRNA and to a core stretch of the same number of nucleotides in the corresponding sense strand. In some embodiments, an antisense strand core stretch is 100% (perfectly) complementary or at least about 85% (substantially) complementary to a nucleotide sequence (*e.g.*, target sequence) of the same length present in the MUC5AC mRNA target. In some embodiments, this antisense strand core stretch is 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In some embodiments, this antisense strand core stretch is 19 nucleotides in length. In some embodiments, this antisense strand core stretch is 17 nucleotides in length. In some embodiments, this antisense strand core stretch is 21 nucleotides in length. A sense strand core stretch sequence can be the same length as a corresponding antisense core stretch sequence or it can be a different length.

[0085] The MUC5AC RNAi agent sense and antisense strands anneal to form a duplex. A sense strand and an antisense strand of a MUC5AC RNAi agent can be partially, substantially, or fully complementary to each other. Within the complementary duplex region, the sense strand core stretch sequence is at least 85% complementary or 100% complementary to the antisense core stretch sequence. In some embodiments, the sense strand core stretch sequence contains a sequence of at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 nucleotides that is at least 85% or 100% complementary to a corresponding 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleotide sequence of the antisense strand core stretch sequence (i.e., the sense and antisense core stretch sequences of a MUC5AC RNAi agent have a region of at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, or at least 24 nucleotides that is at least 85% base paired or 100% base paired.)

[0086] In some embodiments, the antisense strand of a MUC5AC RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 2, Table 3, or Table 11. In some embodiments, the sense strand of a MUC5AC RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0087] In some embodiments, the sense strand and/or the antisense strand can optionally and independently contain an additional 1, 2, 3, 4, 5, or 6 nucleotides (extension) at the 3' end, the 5' end, or both the 3' and 5' ends of the core stretch sequences. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sequence in the MUC5AC mRNA. The sense strand additional nucleotides, if present, may or may not be identical to the corresponding sequence in the MUC5AC mRNA. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sense strand's additional nucleotides, if present.

[0088] As used herein, an extension comprises 1, 2, 3, 4, 5, or 6 nucleotides at the 5' and/or 3' end of the sense strand core stretch sequence and/or antisense strand core stretch sequence. The extension nucleotides on a sense strand may or may not be complementary to nucleotides, either core stretch sequence nucleotides or extension nucleotides, in the corresponding antisense strand. Conversely, the extension nucleotides on an antisense strand may or may not be complementary to nucleotides, either core stretch nucleotides or extension nucleotides, in the corresponding sense strand. In some embodiments, both the sense strand and the antisense strand of an RNAi agent contain 3' and 5' extensions. In some

embodiments, one or more of the 3' extension nucleotides of one strand base pairs with one or more 5' extension nucleotides of the other strand. In other embodiments, one or more of 3' extension nucleotides of one strand do not base pair with one or more 5' extension nucleotides of the other strand. In some embodiments, a MUC5AC RNAi agent has an antisense strand having a 3' extension and a sense strand having a 5' extension. In some embodiments, the extension nucleotide(s) are unpaired and form an overhang. As used herein, an "overhang" refers to an extension or stretch of one or more unpaired nucleotides located at a terminal end of either the sense strand or the antisense strand that does not form part of the hybridized or duplexed portion of an RNAi agent disclosed herein.

[0089] In some embodiments, a MUC5AC RNAi agent comprises an antisense strand having a 3' extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In other embodiments, a MUC5AC RNAi agent comprises an antisense strand having a 3' extension of 1, 2, or 3 nucleotides in length. In some embodiments, one or more of the antisense strand extension nucleotides comprise nucleotides that are complementary to the corresponding MUC5AC mRNA sequence. In some embodiments, one or more of the antisense strand extension nucleotides comprise nucleotides that are not complementary to the corresponding MUC5AC mRNA sequence.

[0090] In some embodiments, a MUC5AC RNAi agent comprises a sense strand having a 3' extension of 1, 2, 3, 4, or 5 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprises adenosine, uracil, or thymidine nucleotides, AT dinucleotide, or nucleotides that correspond to or are the identical to nucleotides in the MUC5AC mRNA sequence. In some embodiments, the 3' sense strand extension includes or consists of one of the following sequences, but is not limited to: T, UT, TT, UU, UUT, TTT, or TTTT (each listed 5' to 3').

[0091] A sense strand can have a 3' extension and/or a 5' extension. In some embodiments, a MUC5AC RNAi agent comprises a sense strand having a 5' extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprise nucleotides that correspond to or are identical to nucleotides in the MUC5AC mRNA sequence.

[0092] Examples of sequences used in forming MUC5AC RNAi agents are provided in Tables 2, 3, 4, 5, 6, 7, and 11. In some embodiments, a MUC5AC RNAi agent antisense strand includes a sequence of any of the sequences in Tables 2, 3, or 11. In certain embodiments, a MUC5AC RNAi agent antisense strand comprises or consists of any one of

the modified sequences in Table 3. In some embodiments, a MUC5AC RNAi agent antisense strand includes the sequence of nucleotides (from 5' end → 3' end) 1-17, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, or 2-21, of any of the sequences in Table 2, Table 3, or Table 11. In some embodiments, a MUC5AC RNAi agent sense strand includes the sequence of any of the sequences in Tables 2, 4, 5, 6, or 7. In some embodiments, a MUC5AC RNAi agent sense strand includes the sequence of nucleotides (from 5' end → 3' end) 1-18, 1-19, 1-20, 1-21, 2-19, 2-20, 2-21, 3-20, 3-21, or 4-21 of any of the sequences in Tables 2, 4, 5, 6, or 7. In certain embodiments, a MUC5AC RNAi agent sense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 4, 5, 6, 7, or 11.

[0093] In some embodiments, the sense and antisense strands of the RNAi agents described herein contain the same number of nucleotides. In some embodiments, the sense and antisense strands of the RNAi agents described herein contain different numbers of nucleotides. In some embodiments, the sense strand 5' end and the antisense strand 3' end of an RNAi agent form a blunt end. In some embodiments, the sense strand 3' end and the antisense strand 5' end of an RNAi agent form a blunt end. In some embodiments, both ends of an RNAi agent form blunt ends. In some embodiments, neither end of an RNAi agent is blunt-ended. As used herein a "blunt end" refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands are complementary (form a complementary base-pair).

[0094] In some embodiments, the sense strand 5' end and the antisense strand 3' end of an RNAi agent form a frayed end. In some embodiments, the sense strand 3' end and the antisense strand 5' end of an RNAi agent form a frayed end. In some embodiments, both ends of an RNAi agent form a frayed end. In some embodiments, neither end of an RNAi agent is a frayed end. As used herein a frayed end refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands form a pair (i.e., do not form an overhang) but are not complementary (i.e. form a non-complementary pair). In some embodiments, one or more unpaired nucleotides at the end of one strand of a double stranded RNAi agent form an overhang. The unpaired nucleotides may be on the sense strand or the antisense strand, creating either 3' or 5' overhangs. In some embodiments, the RNAi agent contains: a blunt end and a frayed end, a blunt end and 5' overhang end, a blunt end and a 3' overhang end, a frayed end and a 5' overhang end, a frayed end and a 3' overhang end, two 5' overhang ends, two 3' overhang ends, a 5' overhang end and a 3'

overhang end, two frayed ends, or two blunt ends. Typically, when present, overhangs are located at the 3' terminal ends of the sense strand, the antisense strand, or both the sense strand and the antisense strand.

[0095] The MUC5AC RNAi agents disclosed herein may also be comprised of one or more modified nucleotides. In some embodiments, substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand of the MUC5AC RNAi agent are modified nucleotides. The MUC5AC RNAi agents disclosed herein may further be comprised of one or more modified internucleoside linkages, e.g., one or more phosphorothioate linkages or phosphorodithioate linkages. In some embodiments, a MUC5AC RNAi agent contains one or more modified nucleotides and one or more modified internucleoside linkages. In some embodiments, a 2'-modified nucleotide is combined with modified internucleoside linkage.

[0096] In some embodiments, a MUC5AC RNAi agent is prepared or provided as a salt, mixed salt, or a free-acid. In some embodiments, a MUC5AC RNAi agent is prepared as a pharmaceutically acceptable salt. In some embodiments, a MUC5AC RNAi agent is prepared as a pharmaceutically acceptable sodium salt. Such forms that are well known in the art are within the scope of the inventions disclosed herein.

Modified Nucleotides

[0097] Modified nucleotides, when used in various oligonucleotide constructs, can preserve activity of the compound in cells while at the same time increasing the serum stability of these compounds, and can also minimize the possibility of activating interferon activity in humans upon administration of the oligonucleotide construct.

[0098] In some embodiments, a MUC5AC RNAi agent contains one or more modified nucleotides. As used herein, a "modified nucleotide" is a nucleotide other than a ribonucleotide (2'-hydroxyl nucleotide). In some embodiments, at least 50% (e.g., at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100%) of the nucleotides are modified nucleotides. As used herein, modified nucleotides can include, but are not limited to, deoxyribonucleotides, nucleotide mimics, abasic nucleotides, 2'-modified nucleotides, inverted nucleotides, modified nucleobase-comprising nucleotides, bridged nucleotides, peptide nucleic acids (PNAs), 2',3'-seco nucleotide mimics (unlocked nucleobase analogues), locked nucleotides, 3'-O-methoxy (2' internucleoside linked) nucleotides, 2'-F-Arabino nucleotides, 5'-Me, 2'-fluoro nucleotide,

morpholino nucleotides, vinyl phosphonate deoxyribonucleotides, vinyl phosphonate containing nucleotides, and cyclopropyl phosphonate containing nucleotides. 2'-modified nucleotides (*i.e.*, a nucleotide with a group other than a hydroxyl group at the 2' position of the five-membered sugar ring) include, but are not limited to, 2'-O-methyl nucleotides (also referred to as 2'-methoxy nucleotides), 2'-fluoro nucleotides (also referred to herein as 2'-deoxy-2'-fluoro nucleotides), 2'-deoxy nucleotides, 2'-methoxyethyl (2'-O-2-methoxyethyl) nucleotides (also referred to as 2'-MOE), 2'-amino nucleotides, and 2'-alkyl nucleotides. It is not necessary for all positions in a given compound to be uniformly modified. Conversely, more than one modification can be incorporated in a single MUC5AC RNAi agent or even in a single nucleotide thereof. The MUC5AC RNAi agent sense strands and antisense strands can be synthesized and/or modified by methods known in the art. Modification at one nucleotide is independent of modification at another nucleotide.

[0099] Modified nucleobases include synthetic and natural nucleobases, such as 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, (e.g., 2-aminopropyladenine, 5-propynyluracil, or 5-propynylcytosine), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, inosine, xanthine, hypoxanthine, 2-aminoadenine, 6-alkyl (e.g., 6-methyl, 6-ethyl, 6-isopropyl, or 6-n-butyl) derivatives of adenine and guanine, 2-alkyl (e.g., 2-methyl, 2-ethyl, 2-isopropyl, or 2-n-butyl) and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, cytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-sulfhydryl, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (e.g., 5-bromo), 5-trifluoromethyl, and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

[0100] In some embodiments, the 5' and/or 3' end of the antisense strand can include abasic residues (Ab), which can also be referred to as an "abasic site" or "abasic nucleotide." An abasic residue (Ab) is a nucleotide or nucleoside that lacks a nucleobase at the 1' position of the sugar moiety. (*See, e.g.*, U.S. Patent No. 5,998,203). In some embodiments, an abasic residue can be placed internally in a nucleotide sequence. In some embodiments, Ab or AbAb can be added to the 3' end of the antisense strand. In some embodiments, the 5' end of the sense strand can include one or more additional abasic residues (e.g., (Ab) or (AbAb)). In some embodiments, UUAb, UAb, or Ab are added to the 3' end of the sense strand. In

some embodiments, an abasic (deoxyribose) residue can be replaced with a ribitol (abasic ribose) residue.

[0101] In some embodiments, all or substantially all of the nucleotides of an RNAi agent are modified nucleotides. As used herein, an RNAi agent wherein substantially all of the nucleotides present are modified nucleotides is an RNAi agent having four or fewer (i.e., 0, 1, 2, 3, or 4) nucleotides in both the sense strand and the antisense strand being ribonucleotides (i.e., unmodified). As used herein, a sense strand wherein substantially all of the nucleotides present are modified nucleotides is a sense strand having two or fewer (i.e., 0, 1, or 2) nucleotides in the sense strand being unmodified ribonucleotides. As used herein, an antisense sense strand wherein substantially all of the nucleotides present are modified nucleotides is an antisense strand having two or fewer (i.e., 0, 1, or 2) nucleotides in the antisense strand being unmodified ribonucleotides. In some embodiments, one or more nucleotides of an RNAi agent is an unmodified ribonucleotide. Chemical structures for certain modified nucleotides are set forth in Table 12 herein.

Modified Internucleoside Linkages

[0102] In some embodiments, one or more nucleotides of a MUC5AC RNAi agent are linked by non-standard linkages or backbones (i.e., modified internucleoside linkages or modified backbones). Modified internucleoside linkages or backbones include, but are not limited to, phosphorothioate groups (represented herein as a lower case “s”), chiral phosphorothioates, thiophosphates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, alkyl phosphonates (e.g., methyl phosphonates or 3'-alkylene phosphonates), chiral phosphonates, phosphinates, phosphoramidates (e.g., 3'-amino phosphoramidate, aminoalkylphosphoramidates, or thionophosphoramidates), thionoalkylphosphonates, thionoalkylphosphotriesters, morpholino linkages, boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of boranophosphates, or boranophosphates having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. In some embodiments, a modified internucleoside linkage or backbone lacks a phosphorus atom. Modified internucleoside linkages lacking a phosphorus atom include, but are not limited to, short chain alkyl or cycloalkyl inter-sugar linkages, mixed heteroatom and alkyl or cycloalkyl inter-sugar linkages, or one or more short chain heteroatomic or heterocyclic inter-sugar linkages. In some embodiments, modified internucleoside backbones include, but are not limited to, siloxane backbones, sulfide

backbones, sulfoxide backbones, sulfone backbones, formacetyl and thioformacetyl backbones, methylene formacetyl and thioformacetyl backbones, alkene-containing backbones, sulfamate backbones, methyleneimino and methylenehydrazino backbones, sulfonate and sulfonamide backbones, amide backbones, and other backbones having mixed N, O, S, and CH₂ components.

[0103] In some embodiments, a sense strand of a MUC5AC RNAi agent can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages, an antisense strand of a MUC5AC RNAi agent can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages. In some embodiments, a sense strand of a MUC5AC RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, an antisense strand of a MUC5AC RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, or 4 phosphorothioate linkages.

[0104] In some embodiments, a MUC5AC RNAi agent sense strand contains at least two phosphorothioate internucleoside linkages. In some embodiments, the phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 3' end of the sense strand. In some embodiments, one phosphorothioate internucleoside linkage is at the 5' end of the sense strand nucleotide sequence, and another phosphorothioate linkage is at the 3' end of the sense strand nucleotide sequence. In some embodiments, two phosphorothioate internucleoside linkage are located at the 5' end of the sense strand, and another phosphorothioate linkage is at the 3' end of the sense strand. In some embodiments, the sense strand does not include any phosphorothioate internucleoside linkages between the nucleotides, but contains one, two, or three phosphorothioate linkages between the terminal nucleotides on both the 5' and 3' ends and the optionally present inverted abasic residue terminal caps. In some embodiments, the targeting ligand is linked to the sense strand via a phosphorothioate linkage.

[0105] In some embodiments, a MUC5AC RNAi agent antisense strand contains four phosphorothioate internucleoside linkages. In some embodiments, the four phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 5' end of the antisense strand and between the nucleotides at positions 19-21, 20-22, 21-23, 22-24, 23-25, or 24-26 from the 5' end. In some embodiments, three phosphorothioate internucleoside linkages are located between positions 1-4 from the 5' end of the antisense strand, and a fourth phosphorothioate internucleoside linkage is located between positions

20-21 from the 5' end of the antisense strand. In some embodiments, a MUC5AC RNAi agent contains at least three or four phosphorothioate internucleoside linkages in the antisense strand.

Capping Residues or Moieties

[0106] In some embodiments, the sense strand may include one or more capping residues or moieties, sometimes referred to in the art as a “cap,” a “terminal cap,” or a “capping residue.” As used herein, a “capping residue” is a non-nucleotide compound or other moiety that can be incorporated at one or more termini of a nucleotide sequence of an RNAi agent disclosed herein. A capping residue can provide the RNAi agent, in some instances, with certain beneficial properties, such as, for example, protection against exonuclease degradation. In some embodiments, inverted abasic residues (invAb) (also referred to in the art as “inverted abasic sites”) are added as capping residues (*see* Table 12). (See, e.g., F. Czauderna, *Nucleic Acids Res.*, 2003, 31(11), 2705-16). Capping residues are generally known in the art, and include, for example, inverted abasic residues as well as carbon chains such as a terminal C₃H₇ (propyl), C₆H₁₃ (hexyl), or C₁₂H₂₅ (dodecyl) groups. In some embodiments, a capping residue is present at either the 5' terminal end, the 3' terminal end, or both the 5' and 3' terminal ends of the sense strand. In some embodiments, the 5' end and/or the 3' end of the sense strand may include more than one inverted abasic deoxyribose moiety as a capping residue.

[0107] In some embodiments, one or more inverted abasic residues (invAb) are added to the 3' end of the sense strand. In some embodiments, one or more inverted abasic residues (invAb) are added to the 5' end of the sense strand. In some embodiments, one or more inverted abasic residues or inverted abasic sites are inserted between the targeting ligand and the nucleotide sequence of the sense strand of the RNAi agent. In some embodiments, the inclusion of one or more inverted abasic residues or inverted abasic sites at or near the terminal end or terminal ends of the sense strand of an RNAi agent allows for enhanced activity or other desired properties of an RNAi agent.

[0108] In some embodiments, one or more inverted abasic residues (invAb) are added to the 5' end of the sense strand. In some embodiments, one or more inverted abasic residues can be inserted between the targeting ligand and the nucleotide sequence of the sense strand of the RNAi agent. The inverted abasic residues may be linked via phosphate, phosphorothioate (e.g., shown herein as (invAb)s)), or other internucleoside linkages. In

some embodiments, the inclusion of one or more inverted abasic residues at or near the terminal end or terminal ends of the sense strand of an RNAi agent may allow for enhanced activity or other desired properties of an RNAi agent. In some embodiments, an inverted abasic (deoxyribose) residue can be replaced with an inverted ribitol (abasic ribose) residue. In some embodiments, the 3' end of the antisense strand core stretch sequence, or the 3' end of the antisense strand sequence, may include an inverted abasic residue. The chemical structures for inverted abasic deoxyribose residues are shown in Table 12 below.

MUC5AC RNAi Agents

[0109] The MUC5AC RNAi agents disclosed herein are designed to target specific positions on a MUC5AC gene (e.g., SEQ ID NO:1 (NM_001304359.2)). As defined herein, an antisense strand sequence is designed to target a MUC5AC gene at a given position on the gene when the 5' terminal nucleobase of the antisense strand is aligned with a position that is 19 nucleotides downstream (towards the 3' end) from the position on the gene when base pairing to the gene. For example, as illustrated in Tables 1 and 2 herein, an antisense strand sequence designed to target a MUC5AC gene at position 3535 requires that when base pairing to the gene, the 5' terminal nucleobase of the antisense strand is aligned with position 3553 of a MUC5AC gene.

[0110] As provided herein, a MUC5AC RNAi agent does not require that the nucleobase at position 1 (5' → 3') of the antisense strand be complementary to the gene, provided that there is at least 85% complementarity (e.g., at least 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% complementarity) of the antisense strand and the gene across a core stretch sequence of at least 16 consecutive nucleotides. For example, for a MUC5AC RNAi agent disclosed herein that is designed to target position 3535 of a MUC5AC gene, the 5' terminal nucleobase of the antisense strand of the of the MUC5AC RNAi agent must be aligned with position 3553 of the gene; however, the 5' terminal nucleobase of the antisense strand may be, but is not required to be, complementary to position 3553 of a MUC5AC gene, provided that there is at least 85% complementarity (e.g., at least 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% complementarity) of the antisense strand and the gene across a core stretch sequence of at least 16 consecutive nucleotides. As shown by, among other things, the various examples disclosed herein, the specific site of binding of the gene by the antisense strand of the MUC5AC RNAi agent (e.g., whether the MUC5AC RNAi agent is designed to target a MUC5AC gene at position 3535, at position 4993, at

position 15051, or at some other position) is an important factor to the level of inhibition achieved by the MUC5AC RNAi agent. (*See also*, Kamola et al., *The siRNA Non-seed Region and Its Target Sequences are Auxiliary Determinants of Off-Target Effects*, PLOS Computational Biology, 11(12), Figure 1 (2015)).

[0111] In some embodiments, the MUC5AC RNAi agents disclosed herein target a MUC5AC gene at or near the positions of the MUC5AC sequence shown in Table 1. In some embodiments, the antisense strand of a MUC5AC RNAi agent disclosed herein includes a core stretch sequence that is fully, substantially, or at least partially complementary to a target MUC5AC 19-mer sequence disclosed in Table 1.

Table 1. MUC5AC 19-mer mRNA Target Sequences (taken from *homo sapiens* mucin 5AC, oligomeric mucus/gel-forming (MUC5AC) gene transcript, GenBank NM_001304359.2 (SEQ ID NO:1))

SEQ ID No.	MUC5AC 19-mer Target Sequences (5' → 3')	Corresponding Positions of Sequence on SEQ ID NO: 1	Targeted Gene Position (as referred to herein)
2	GCUUCCACUACAAGACCUU	304-322	304
3	UGUGGAACCACGAUGACAG	610-628	610
4	GCAAGACCUCUGCUUCUGU	923-941	923
5	CACAGACUGCACCAACUGC	1277-1295	1277
6	CAGUGCCUUCACUGUACUG	1445-1463	1445
7	AGUGCCUUCACUGUACUGC	1446-1464	1446
8	CAGCGAGACCUGCCUGAAG	1493-1511	1493
9	GGGAAGUGUCCUGAACCA	1567-1585	1567
10	AACGUCACCAUCUUCAGAC	1617-1635	1617
11	ACGUCACCAUCUUCAGACC	1618-1636	1618
12	UGUGGGAACUUAACAGCA	1758-1776	1758
13	GGGAACUUAACAGCAUCC	1761-1779	1761
14	UCCAGGCCGAUGACUCCG	1777-1795	1777
15	CUUCUUAACACCUUCAAG	1832-1850	1832
16	UUCAACACCUUCAAGACCC	1836-1854	1836
17	CCAACAUCAGGAACAGCUU	1867-1885	1867
18	CAUCAGGAACAGCUUCGAG	1871-1889	1871
19	AGUAUGCUCAGCACUGGUG	1921-1939	1921
20	ACCUACUACUCGAACUGCA	2001-2019	2001
21	UACUACUCGAACUGCAUGU	2004-2022	2004
22	ACAUCACCUGCAGUGUUGG	2230-2248	2230
23	CACCUGCAGUGUUGGCUUC	2234-2252	2234
24	UGGACAUGACCUGUUACAG	2536-2554	2536
25	AGAGCUACAGCUUCAACGG	2797-2815	2797
26	AGGGACCACCUGCUCCAAG	2915-2933	2915

SEQ ID No.	MUC5AC 19-mer Target Sequences (5' → 3')	Corresponding Positions of Sequence on SEQ ID NO: 1	Targeted Gene Position (as referred to herein)
27	CUGCUGCAAGGCCAUC AAG	2924-2942	2924
28	UGCUGCAAGGCCAUC AAGA	2925-2943	2925
29	CUGCAAGGCCAUC AAGAUU	2927-2945	2927
30	GACAAGAAGACCAGCAUCU	3090-3108	3090
31	AGACCAGCAUCUUC AUCAA	3097-3115	3097
32	ACCAGCAUCUUC AUC AACC	3099-3117	3099
33	CCUCAGCCCCGAGUUC AAG	3116-3134	3116
34	UGGGAACUUCGACGACAUC	3155-3173	3155
35	CAGAAGCAGUGCAGCAUCC	3321-3339	3321
36	CAGGCCUGCCAUGAAGUUU	3475-3493	3475
37	CCCUCUGUUCUGCGACUAC	3530-3548	3530
38	CCUCUGUUCUGCGACUACU	3531-3549	3531
39	UCUGUUCUGCGACUACUAC	3533-3551	3533
40	CUGUUCUGCGACUACUACA	3534-3552	3534
41	UGUUCUGCGACUACUACAA	3535-3553	3535
42	UCUUUGAUGAGGACAAGAU	3694-3712	3694
43	CUUUGAUGAGGACAAGAUG	3695-3713	3695
44	UUUGAUGAGGACAAGAUGC	3696-3714	3696
45	ACGUCAUCUACCACACGAC	3910-3928	3910
46	UGCUACAACUACCAGAUCA	4443-4461	4443
47	UACAACUACCAGAUCAGGG	4446-4464	4446
48	CUGAUUUGCCUGAACAAGA	4992-5010	4992
49	UGAUUUGCCUGAACAAGAA	4993-5011	4993
50	CACCCAUCUGCUACAACUA	5020-5038	5020
51	ACCCAUCUGCUACAACUAU	5021-5039	5021
52	UGCUACAACUAUGAGAUCC	5028-5046	5028
53	GCUACAACUAUGAGAUCCG	5029-5047	5029
54	GAUCCGCAUCCAGUGUUGC	5042-5060	5042
55	AAAGUGGUUCGACGUGGAC	5297-5315	5297
56	GUGGUUCGACGUGGACUUC	5300-5318	5300
57	GGUUCGACGUGGACUCCC	5302-5320	5302
58	AAGGAAACCUACAACAACA	5346-5364	5346
59	AGGAAACCUACAACAACAU	5347-5365	5347
60	AAACCUACAACAACAUCAU	5350-5368	5350
61	AGAGGUGAGCAUCGAACAC	5441-5459	5441
62	GCAGGGACCCUUCAAGAUG	5519-5537	5519
63	AGAUGUGCCUCAACUACGA	5533-5551	5533
64	AUGUGCCUCAACUACGAGG	5535-5553	5535
65	ACCUCUCUUGGCAGAAAU	6777-6795	6777
66	AGGACAACCACUUUGGUGA	6798-6816	6798
67	CUCUGCUCCUACAACUAGC	6998-7016	6998
68	ACCUCUGCUUCUACAACUA	7980-7998	7980
69	AUAACCAGCACAAUCUUCUG	8448-8466	8448

SEQ ID No.	MUC5AC 19-mer Target Sequences (5' → 3')	Corresponding Positions of Sequence on SEQ ID NO: 1	Targeted Gene Position (as referred to herein)
70	ACCAGAACCAACCUCUGCUC	8739-8757	8739
71	CUACAACCAGCACAAUCUC	9310-9328	9310
72	UGGACCAAGUGGUUUGACA	9729-9747	9729
73	ACAACCAGCACAAUCUCUG	10206-10224	10206
74	CAACCACUUUGGUGACAAG	11014-11032	11014
75	ACAACCAACACAACUUCUG	11361-11379	11361
76	CUCUGCUCCUACAACUAGC	12965-12983	12965
77	GAGAUCAUCUUAACAACA	15051-15069	15051
78	AGAUCUUCUUAACAACAA	15052-15070	15052

[0112] *Homo sapiens* mucin 5AC, oligomeric mucus/gel-forming (MUC5AC) gene transcript, GenBank NM_001304359.2 (SEQ ID NO:1) (17,448 bases):

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1  ctcagaggct gctgaggac agggcactct tccccgcctt ccacacaatg agtgttgcc
61  ggaggaagct ggccctgtct tggccctgg ctctcgtctt ggcctgcacc cggcatacag
121 gcatgccca gcatggctcc tcgaaatcca gctacaagca ccacctgcc ctctctccta
181 tcgcccgggg gccccagcggg gtcccgtccc gtggggcgac tgtcttccca tctctgagga
241 ccatccctgt ggtacgagcc tccaaccggg cgcacaacgg gcgggtgtgc agcacctggg
301 gcagcttcca ctacaagacc ttgacggcg acgtcttccg ctccccggc ctctgcaact
361 acgtgttctc cgagcactgc ggtgccgctt acgaggattt taacatccag ctacgccgca
421 gccaggagtc agcggccccc acgtgagca gggctctcat gaaggtggat ggcgtgggtca
481 tccagctgac caagggtccc gtcttggtca acggccaccc ggtcctgtct cccttcagcc
541 agtctggggt cctcattcag cagagcagca gctacaccaa ggtggaggcc aggtctgggg
601 ttgtctcat gtggaaccac gatgacagcc tgctgctgga gctggacacc aaatacgcca
661 acaagacctg tgggctctgt ggggacttca acgggatgcc cgtggtcagc gagctctctt
721 cccacaacac caagctgaca cccatggaat tcgggaacct gcagaagatg gacgacccca
781 cggaccagtg tcaggacctt gtcctgaac ccccgaggaa ctgtccactt ggctttggca
841 tctgtgagga gctcctgcac ggccagctgt tcttggtctg cgtggccctg gtggacgtcg
901 gcagctacct ggaggcttgc aggaagacc tctgcttctg tgaagacacc gacctgtca
961 gctgcgtctg ccacacctt gccagttact cccggcagtg caccatgca ggggggttgc
1021 cccaggactg gcggggccct gacttctgcc cccagaagtg cccaacaac atgcagtacc
1081 acgagtgcgc ctccccctgc gcagacacct gctcaacca ggagcactcc cgggcctgtg
1141 aggaccactg tgtggccggc tcttctgcc ctgaggggac ggtgcttgac gacatcgccc
1201 agaccggctg tctcctgtg tcaaagtgtg cctgcgtcta caacggggct gcctatgccc

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1261 cagggggccac ctactccaca gactgcacca actgcacctg ctccggaggc cgggtggagct
1321 gccaggaggt tccatgcccc ggtacctgct ctgtgcttgg aggtgcccac ttctcaacgt
1381 ttgacgggaa gcaatacacg gtgcacggcg actgcagcta tgtgctgacc aagccctgtg
1441 acagcagtgc ctactactga ctggctgagc tgcgcagggt cgggctgacg gacagcgaga
1501 cctgcctgaa gagcgtgaca ctgagcctgg atggggcgca gacggtggtg gtgatcaagg
1561 ccagtgggga agtgttcctg aaccagatct acaccagct gcccatctct gcagccaacg
1621 tcaccatctt cagacctca accttcttca tcatcgcca gaccagcctg ggcctgcagc
1681 tgaacctgca gctggtgccc accatgcagc tgttcatgca gctggcgccc aagctccgtg
1741 ggcagacctg cggctctgtt ggggaactca acagcatcca ggccgatgac ttccggaccg
1801 tcagtggggg ggtggaggcc accgctgcgg ccttcttcaa caccttcaag acccaggccc
1861 cctgcccaca catcaggaac agcttcgagg acccctgctc tctgagcgtg gagaatgaga
1921 agtatgtca gactgggtgc tcgcagctga ccgatgccga cggcccttc ggccggtgccc
1981 atgtgccgt gaagccggga acctactact cgaactgcat gtttgacacc tgcaactgtg
2041 agcggagcga ggactgcctg tgcgccgcg tctctccta cgtgcacgcc tgtgccgcca
2101 agggcggtga gctcggcgcc tggaggagac gcgtctgcac gaagcctatg accacttggc
2161 ccaagtcaat gacgtaccac taccatgtca gcacctgcca gcccacctgc cgtccctga
2221 gcgaggggga catcacctgc agtgttggct tcacccccgt ggatggctgc atctgtccca
2281 agggcacctt cctggacgac acgggcaagt gtgtgcagc cagcaactgt cctgtctacc
2341 acagaggctc catgatcccc aatggggagt cggtgacga cagcggggct atctgcacct
2401 gcacacatgg gaagctgagc tgcacggag gcccaagccc cggccagtg tgtgtgcgc
2461 ccatggtgtt ctttgactgc cgaaatgcca cggccgggga cacaggggct ggctgtcaga
2521 agagctgcca cacactggac atgacctgtt acagcccca gtgtgtgctt ggctgcgtgt
2581 gcccgcaggg gctggtggcg gacggcgagg gcggctgcat cactgcggag gactgccctt
2641 gcgtgcaca tggggccagc taccgggccg gccagacct cgggtgggc tgcaaacct
2701 gcacctgtga cagcaggatg tggcggtgca cagatgacct ctgctggcc acctgcgccg
2761 tgtacgggga cggccactac ctacacttcg acggacagag ctacagcttc aacggagact
2821 gcgagtacac gctggtgcag aacctgtgt gcgggaaaga cagcaccag gactccttc
2881 gtgtgttac cgagaacgtc cctgcggca ccacaggac cacctgtctc aaggccatca
2941 agattttctt ggggggcttc gagctgaagc taagccatgg gaaggtggag gtgatcggga
3001 cggacgagag ccaggaggtg ccatacacca tccggcagat gggcatctac ctggtggtgg
3061 acaccgacat tggcctggtg ctgctgtggg acaagaagac cagcatcttc atcaacctca
3121 gcccagagt caaggcgagg gtctgcggcc tgtgtgggaa ctgcagac atcgccgtta
3181 atgactttgc cagcggagc cggctctgtg tgggggacgt gctggagttt gggaacagct

3241 ggaagctctc cccctcctgc ccagatgcc tggcgcccaa ggaccctgc acggccaacc
3301 ccttccgcaa gtcctgggcc cagaagcagt gcagcatcct ccacggcccc accttcgccg
3361 cctgccacgc acacgtggag ccggccaggc actacgaggc ctgcgtgaac gacgcgtgcg
3421 cctgcgactc cgggggtgac tgcgagtct tctgcacggc tctggccgcc tacgccagg
3481 cctgccatga agtaggcctg tgtgtgtctt ggccggacccc gagcatctgc cctctgttct
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[0113] In some embodiments, a MUC5AC RNAi agent includes an antisense strand wherein position 19 of the antisense strand (5'→3') is capable of forming a base pair with position 1 of a 19-mer target sequence disclosed in Table 1. In some embodiments, a MUC5AC agent includes an antisense strand wherein position 1 of the antisense strand (5'→3') is capable of forming a base pair with position 19 of a 19-mer target sequence disclosed in Table 1.

[0114] In some embodiments, a MUC5AC agent includes an antisense strand wherein position 2 of the antisense strand (5' → 3') is capable of forming a base pair with position 18 of a 19-mer target sequence disclosed in Table 1. In some embodiments, a MUC5AC agent includes an antisense strand wherein positions 2 through 18 of the antisense strand (5' → 3') are capable of forming base pairs with each of the respective complementary bases located at positions 18 through 2 of the 19-mer target sequence disclosed in Table 1.

[0115] For the RNAi agents disclosed herein, the nucleotide at position 1 of the antisense strand (from 5' end → 3' end) can be perfectly complementary to a MUC5AC gene, or can be non-complementary to a MUC5AC gene. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5' end → 3' end) is a U, A, or dT. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5' end → 3' end) forms an A:U or U:A base pair with the sense strand.

[0116] In some embodiments, a MUC5AC RNAi agent antisense strand comprises the sequence of nucleotides (from 5' end → 3' end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2, Table 3, or Table 11. In some embodiments, a MUC5AC RNAi sense strand comprises the sequence of nucleotides (from 5' end → 3' end) 1-17, 1-18, or 2-18 of any of the sense strand sequences in Table 2, Table 4, Table 5, Table 6, or Table 7.

[0117] In some embodiments, a MUC5AC RNAi agent is comprised of (i) an antisense strand comprising the sequence of nucleotides (from 5' end → 3' end) 1-18, 1-19, or 2-19 of any of the antisense strand sequences in Table 2 or Table 3, and (ii) a sense strand

comprising the sequence of nucleotides (from 5' end → 3' end) 2-19, 1-19, 1-18, or 2-18 of any of the sense strand sequences in Table 2, Table 4, Table 5, Table 6, or Table 7.

[0118] In some embodiments, the MUC5AC RNAi agents include core 19-mer nucleotide sequences shown in the following Table 2.

Table 2. MUC5AC RNAi Agent Antisense Strand and Sense Strand Core Stretch Base Sequences (N=any nucleobase; I = inosine (hypoxanthine nucleobase))

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
79	UUGUAGUAGUCGCAGAACAA	568	UGUUCUGCGACUACUACAA	3535-3553	3535
80	NUGUAGUAGUCGCAGAACAA	569	UGUUCUGCGACUACUACAN	3535-3553	3535
81	UUGUAGUAGUCGCAGAACN	570	NGUUCUGCGACUACUACAA	3535-3553	3535
82	NUGUAGUAGUCGCAGAACN	571	NGUUCUGCGACUACUACAN	3535-3553	3535
83	UUCUUGUUCAGGCAGAAUCA	572	UGAUUUGCCUGAACAAAGAA	4993-5011	4993
84	NUCUUGUUCAGGCAGAAUCA	573	UGAUUUGCCUGAACAAAGAN	4993-5011	4993
85	UUCUUGUUCAGGCAGAAUCN	574	NGAUUUGCCUGAACAAAGAA	4993-5011	4993
86	NUCUUGUUCAGGCAGAAUCN	575	NGAUUUGCCUGAACAAAGAN	4993-5011	4993
87	CUUGAUGGCCUUGGAGCAG	576	CUGCUCCAAGGCCAUCAAG	2924-2942	2924
88	UUUGAUGGCCUUGGAGCAG	577	CUGCUCCAAGGCCAUCAAA	2924-2942	2924
89	NUUGAUGGCCUUGGAGCAG	578	CUGCUCCAAGGCCAUCAAN	2924-2942	2924
90	UUUGAUGGCCUUGGAGCAN	579	NUGCUCCAAGGCCAUCAAA	2924-2942	2924
91	NUUGAUGGCCUUGGAGCAN	580	NUGCUCCAAGGCCAUCAAN	2924-2942	2924
92	AAUCUUGAUGGCCUUGGAG	581	CUCCAAGGCCAUCAAGAUU	2927-2945	2927
93	AAUCUUGAUGGCCUUGGAN	582	NUCCAAGGCCAUCAAGAUU	2927-2945	2927
94	UAUCUUGAUGGCCUUGGAG	583	CUCCAAGGCCAUCAAGAU	2927-2945	2927
95	UAUCUUGAUGGCCUUGGAN	584	NUCCAAGGCCAUCAAGAU	2927-2945	2927
96	NAUCUUGAUGGCCUUGGAG	585	CUCCAAGGCCAUCAAGAU	2927-2945	2927
97	NAUCUUGAUGGCCUUGGAN	586	NUCCAAGGCCAUCAAGAU	2927-2945	2927
98	CUUGAACUCGGGGCUGAGG	587	CCUCAGCCCCCGAGUUCAG	3116-3134	3116

SEQ ID NO.: Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.: Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
99 UUUGAACUCGGGGCUGAGG	588 CCUCAGCCCCGAGUUCAAA	3116-3134	3116
100 NUUGAACUCGGGGCUGAGG	589 CCUCAGCCCCGAGUUCAAAN	3116-3134	3116
101 UUUGAACUCGGGGCUGAGN	590 NCUCAGCCCCGAGUUCAAA	3116-3134	3116
102 NUUGAACUCGGGGCUGAGN	591 NCUCAGCCCCGAGUUCAAAN	3116-3134	3116
103 GGAUGCUGCACUGCUCUG	592 CAGAAGCAGUGCAGCAUCC	3321-3339	3321
104 UGAUGCUGCACUGCUCUG	593 CAGAAGCAGUGCAGCAUCA	3321-3339	3321
105 NGAUGCUGCACUGCUCUG	594 CAGAAGCAGUGCAGCAUCN	3321-3339	3321
106 UGAUGCUGCACUGCUCUN	595 NAGAAGCAGUGCAGCAUCA	3321-3339	3321
107 NGAUGCUGCACUGCUCUN	596 NAGAAGCAGUGCAGCAUCN	3321-3339	3321
108 UGAUGCUGCACUGCUCUG	597 CAGAAGCAGUGCAGCAUCA	3321-3339	3321
109 UGAUGCUGCACUGCUCUN	598 NAGAAGCAGUGCAGCAUCA	3321-3339	3321
110 NGAUGCUGCACUGCUCUG	599 CAGAAGCAGUGCAGCAUCN	3321-3339	3321
111 NGAUGCUGCACUGCUCUN	600 NAGAAGCAGUGCAGCAUCN	3321-3339	3321
112 GUAGUCGCAGAACAGAGGG	601 CCCUCUGUUCUGCGACUAC	3530-3548	3530
113 UUAGUCGCAGAACAGAGGG	602 CCCUCUGUUCUGCGACUAA	3530-3548	3530
114 UUAGUCGCAGAACAGAGGN	603 NCCUCUGUUCUGCGACUAA	3530-3548	3530
115 NUAGUCGCAGAACAGAGGG	604 CCCUCUGUUCUGCGACUAN	3530-3548	3530
116 NUAGUCGCAGAACAGAGGN	605 NCCUCUGUUCUGCGACUAN	3530-3548	3530
117 UUAGUCGCAGAACAGAGGG	606 CCCUCUGUUCUGCGIACUAA	3530-3548	3530
118 UUAGUCGCAGAACAGAGGN	607 NCCUCUGUUCUGCGIACUAA	3530-3548	3530
119 NUAGUCGCAGAACAGAGGG	608 CCCUCUGUUCUGCGIACUAN	3530-3548	3530
120 NUAGUCGCAGAACAGAGGN	609 NCCUCUGUUCUGCGIACUAN	3530-3548	3530

SEQ ID NO:.	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO:.	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
121	AGUAGUCGCAGAACAGAGG	610	CCUCUGUUCUGCGACUACU	3531-3549	3531
122	AGUAGUCGCAGAACAGAGN	611	NCUCUGUUCUGCGACUACU	3531-3549	3531
123	UGUAGUCGCAGAACAGAGG	612	CCUCUGUUCUGCGACUACA	3531-3549	3531
124	UGUAGUCGCAGAACAGAGN	613	NCUCUGUUCUGCGACUACA	3531-3549	3531
125	NGUAGUCGCAGAACAGAGG	614	CCUCUGUUCUGCGACUACN	3531-3549	3531
126	NGUAGUCGCAGAACAGAGN	615	NCUCUGUUCUGCGACUACN	3531-3549	3531
127	AGUAGUCGCAGAACAGAGG	616	CCUCUGUUCUICGACUACU	3531-3549	3531
128	AGUAGUCGCAGAACAGAGN	617	NCUCUGUUCUICGACUACU	3531-3549	3531
129	UGUAGUCGCAGAACAGAGG	618	CCUCUGUUCUICGACUACA	3531-3549	3531
130	UGUAGUCGCAGAACAGAGN	619	NCUCUGUUCUICGACUACA	3531-3549	3531
131	NGUAGUCGCAGAACAGAGG	620	CCUCUGUUCUICGACUACN	3531-3549	3531
132	NGUAGUCGCAGAACAGAGN	621	NCUCUGUUCUICGACUACN	3531-3549	3531
133	GUAGUAGUCGAGAACAGA	622	UCUGUUCUGCGACUACUAC	3533-3551	3533
134	UUAGUAGUCGAGAACAGA	623	UCUGUUCUGCGACUACUAA	3533-3551	3533
135	NUAGUAGUCGAGAACAGA	624	UCUGUUCUGCGACUACUAN	3533-3551	3533
136	NUAGUAGUCGAGAACAGN	625	NCUGUUCUGCGACUACUAN	3533-3551	3533
137	UGUAGUAGUCGAGAACAG	626	CUGUUCUGCGACUACUACA	3534-3552	3534
138	NGUAGUAGUCGAGAACAG	627	CUGUUCUGCGACUACUACN	3534-3552	3534
139	NGUAGUAGUCGAGAACAN	628	NUGUUCUGCGACUACUACN	3534-3552	3534
140	AUAGUUGUAGCAGAUUGGU	629	ACCCAUUCUGCUACAACUAAU	5021-5039	5021
141	AUAGUUGUAGCAGAUUGGN	630	NCCCAUUCUGCUACAACUAAU	5021-5039	5021
142	UUAGUUGUAGCAGAUUGGU	631	ACCCAUUCUGCUACAACUAA	5021-5039	5021

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
143	UUAGUUUAGCAGAUUGGN	632	NCCCAUUCUGCUACAACUAA	5021-5039	5021
144	NUAGUUUAGCAGAUUGGU	633	ACCCAUUCUGCUACAACUAN	5021-5039	5021
145	NUAGUUUAGCAGAUUGGN	634	NCCCAUUCUGCUACAACUAN	5021-5039	5021
146	GUCCACGUCGAACCAUUU	635	AAAGUGGUUCGACGUGGAC	5297-5315	5297
147	UCCACGUCGAACCAUUU	636	AAAGUGGUUCGACGUGGAA	5297-5315	5297
148	UCCACGUCGAACCACUUN	637	NAAGUGGUUCGACGUGGAA	5297-5315	5297
149	NUCCACGUCGAACCAUUU	638	AAAGUGGUUCGACGUGGAN	5297-5315	5297
150	NUCCACGUCGAACCACUUN	639	NAAGUGGUUCGACGUGGAN	5297-5315	5297
151	UCCACGUCGAACCAUUU	640	AAAGUGGUUCGACIUGGAA	5297-5315	5297
152	UCCACGUCGAACCACUUN	641	NAAGUGGUUCGACIUGGAA	5297-5315	5297
153	NUCCACGUCGAACCAUUU	642	AAAGUGGUUCGACIUGGAN	5297-5315	5297
154	NUCCACGUCGAACCACUUN	643	NAAGUGGUUCGACIUGGAN	5297-5315	5297
155	GAAGUCCACGUCGAACCCAC	644	GUGGUUCGACGUGGACUUC	5300-5318	5300
156	UAGUCCACGUCGAACCCAC	645	GUGGUUCGACGUGGACUUA	5300-5318	5300
157	UAGUCCACGUCGAACCCAN	646	NUGGUUCGACGUGGACUUA	5300-5318	5300
158	NAAGUCCACGUCGAACCCAC	647	GUGGUUCGACGUGGACUUN	5300-5318	5300
159	NAAGUCCACGUCGAACCCAN	648	NUGGUUCGACGUGGACUUN	5300-5318	5300
160	UAGUCCACGUCGAACCCAC	649	GUGGUUCGACGUGIACUUA	5300-5318	5300
161	UAGUCCACGUCGAACCCAN	650	NUGGUUCGACGUGIACUUA	5300-5318	5300
162	NAAGUCCACGUCGAACCCAC	651	GUGGUUCGACGUGIACUUN	5300-5318	5300
163	NAAGUCCACGUCGAACCCAN	652	NUGGUUCGACGUGIACUUN	5300-5318	5300
164	GGGAAGUCCACGUCGAACC	653	GGUUCGACGUGGACUUC	5302-5320	5302

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
165	UGGAAGUCCACGUCGAACC	654	GGUUCGACGUGGACUUCUA	5302-5320	5302
166	UGGAAGUCCACGUCGAACN	655	NGUUCGACGUGGACUUCUA	5302-5320	5302
167	NGGAAGUCCACGUCGAACC	656	GGUUCGACGUGGACUUCN	5302-5320	5302
168	NGGAAGUCCACGUCGAACN	657	NGUUCGACGUGGACUUCN	5302-5320	5302
169	UGGAAGUCCACGUCGAACC	658	GGUUCGACGUGGACUUCUA	5302-5320	5302
170	UGGAAGUCCACGUCGAACN	659	NGUUCGACGUGGACUUCUA	5302-5320	5302
171	NGGAAGUCCACGUCGAACC	660	GGUUCGACGUGGACUUCN	5302-5320	5302
172	NGGAAGUCCACGUCGAACN	661	NGUUCGACGUGGACUUCN	5302-5320	5302
173	AGAUGCUGGUCUUCUUGUC	662	GACAAGAAGACCAAGCAUCU	3090-3108	3090
174	AGAUGCUGGUCUUCUUGUN	663	NACAAGAAGACCAAGCAUCU	3090-3108	3090
175	UGAUGCUGGUCUUCUUGUC	664	GACAAGAAGACCAAGCAUCA	3090-3108	3090
176	UGAUGCUGGUCUUCUUGUN	665	NACAAGAAGACCAAGCAUCA	3090-3108	3090
177	NGAUGCUGGUCUUCUUGUC	666	GACAAGAAGACCAAGCAUCN	3090-3108	3090
178	NGAUGCUGGUCUUCUUGUN	667	NACAAGAAGACCAAGCAUCN	3090-3108	3090
179	AGAUGCUGGUCUUCUUGUC	668	GACAAGAAGACCAAGCAUCU	3090-3108	3090
180	AGAUGCUGGUCUUCUUGUN	669	NACAAGAAGACCAAGCAUCU	3090-3108	3090
181	UGAUGCUGGUCUUCUUGUC	670	GACAAGAAGACCAAGCAUCA	3090-3108	3090
182	UGAUGCUGGUCUUCUUGUN	671	NACAAGAAGACCAAGCAUCA	3090-3108	3090
183	NGAUGCUGGUCUUCUUGUC	672	GACAAGAAGACCAAGCAUCN	3090-3108	3090
184	NGAUGCUGGUCUUCUUGUN	673	NACAAGAAGACCAAGCAUCN	3090-3108	3090
185	GGUUGAUGAAGCUGGUC	674	ACCAGCAUCUUCACCAACC	3099-3117	3099
186	UGUUGAUGAAGCUGGUN	675	NCCAGCAUCUUCACCAACC	3099-3117	3099

SEQ ID NO.: Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.: Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
187 NGUUGAUGAAGCUGGU	676 ACCAGCAUCUUCUACAACN	3099-3117	3099
188 NGUUGAUGAAGCUGGN	677 NCCAGCAUCUUCUACAACN	3099-3117	3099
189 AUGUUGUUGAGGUUCCU	678 AGGAAACCUACAAACAACU	5347-5365	5347
190 AUGUUGUUGAGGUUCCN	679 NGGAAACCUACAAACAACU	5347-5365	5347
191 UUGUUGUUGAGGUUCCU	680 AGGAAACCUACAAACAACAA	5347-5365	5347
192 UUGUUGUUGAGGUUCCN	681 NGGAAACCUACAAACAACAA	5347-5365	5347
193 NUGUUGUUGAGGUUCCN	682 NGGAAACCUACAAACAACAN	5347-5365	5347
194 AUGUUGUUGUAGGUUU	683 AAACCUACAACAACAUCAU	5350-5368	5350
195 AUGUUGUUGUAGGUUN	684 NAACCUACAACAACAUCAU	5350-5368	5350
196 UUGUUGUUGUAGGUUU	685 AAACCUACAACAACAUCAA	5350-5368	5350
197 UUGUUGUUGUAGGUUN	686 NAACCUACAACAACAUCAA	5350-5368	5350
198 NUGUUGUUGUAGGUUN	687 NAACCUACAACAACAUCAN	5350-5368	5350
199 UUGAUGAAGCUGGUCU	688 AGACCAGCAUCUUCUACAACAA	3097-3115	3097
200 UUGAUGAAGCUGGUCN	689 NGACCAGCAUCUUCUACAACAA	3097-3115	3097
201 NUGAUGAAGCUGGUCU	690 AGACCAGCAUCUUCUACAUCAN	3097-3115	3097
202 NUGAUGAAGCUGGUCN	691 NGACCAGCAUCUUCUACAUCAN	3097-3115	3097
203 UGAUCUGGUAGUUGUAGCA	692 UGCUACAACUACCAAGAUCA	4443-4461	4443
204 UGAUCUGGUAGUUGUAGCN	693 NGCUACAACUACCAAGAUCA	4443-4461	4443
205 NGAUCUGGUAGUUGUAGCA	694 UGCUACAACUACCAAGAUCCN	4443-4461	4443
206 NGAUCUGGUAGUUGUAGCN	695 NGCUACAACUACCAAGAUCCN	4443-4461	4443
207 UGAUCUGGUAGUUGUAGCN	696 NGCUACAACUACCAIAUCA	4443-4461	4443
208 NGAUCUGGUAGUUGUAGCA	697 UGCUACAACUACCAIAUCN	4443-4461	4443

SEQ ID NO.: Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.: Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
209	NGAUCUGGUAGUAGCN	4443-4461	4443
210	UGAUCUGGUAGUAGCN	4443-4461	4443
211	CCCUGAUCUGGUAGUAGUA	4446-4464	4446
212	UCCUGAUCUGGUAGUAGUA	4446-4464	4446
213	NCCUGAUCUGGUAGUAGUA	4446-4464	4446
214	UCCUGAUCUGGUAGUAGUN	4446-4464	4446
215	NCCUGAUCUGGUAGUAGUN	4446-4464	4446
216	CCCUGAUCUGGUAGUAGUA	4446-4464	4446
217	UCCUGAUCUGGUAGUAGUA	4446-4464	4446
218	NCCUGAUCUGGUAGUAGUA	4446-4464	4446
219	UCCUGAUCUGGUAGUAGUN	4446-4464	4446
220	NCCUGAUCUGGUAGUAGUN	4446-4464	4446
221	UAGUUGUAGCAGAUUGGUG	5020-5038	5020
222	NAGUUGUAGCAGAUUGGUG	5020-5038	5020
223	UAGUUGUAGCAGAUUGGUG	5020-5038	5020
224	NAGUUGUAGCAGAUUGGUG	5020-5038	5020
225	GCAACACUGGGAUGCGGAUC	5042-5060	5042
226	UCAACACUGGGAUGCGGAUC	5042-5060	5042
227	NCAACACUGGGAUGCGGAUC	5042-5060	5042
228	UCAACACUGGGAUGCGGAUN	5042-5060	5042
229	NCAACACUGGGAUGCGGAUN	5042-5060	5042
230	GCAACACUGGGAUGCGGAUC	5042-5060	5042

SEQ ID NO:.	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO:.	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
231	UCAAACACUGGGAUGCGGAUC	720	GAUCCGCAUCCAGUUIUGA	5042-5060	5042
232	NCAACACUGGGAUGCGGAUC	721	GAUCCGCAUCCAGUUIUGA	5042-5060	5042
233	UCAAACACUGGGAUGCGGAUN	722	NAUCCGCAUCCAGUUIUGN	5042-5060	5042
234	NCAACACUGGGAUGCGGAUN	723	NAUCCGCAUCCAGUUIUGN	5042-5060	5042
235	GUGUUCGAUGCUCACCCUCU	724	AGAGGUGAGCAUCGAAACAC	5441-5459	5441
236	UUGUUCGAUGCUCACCCUCU	725	AGAGGUGAGCAUCGAAACAA	5441-5459	5441
237	NUGUUCGAUGCUCACCCUCU	726	AGAGGUGAGCAUCGAAACAN	5441-5459	5441
238	UUGUUCGAUGCUCACCCUCN	727	NGAGGUGAGCAUCGAAACAA	5441-5459	5441
239	NUGUUCGAUGCUCACCCUCN	728	NGAGGUGAGCAUCGAAACAN	5441-5459	5441
240	GUGUUCGAUGCUCACCCUCU	729	AGAGGUGAGCAUCIAACAC	5441-5459	5441
241	UUGUUCGAUGCUCACCCUCU	730	AGAGGUGAGCAUCIAACAA	5441-5459	5441
242	NUGUUCGAUGCUCACCCUCU	731	AGAGGUGAGCAUCIAACAN	5441-5459	5441
243	UUGUUCGAUGCUCACCCUCN	732	NGAGGUGAGCAUCIAACAA	5441-5459	5441
244	NUGUUCGAUGCUCACCCUCN	733	NGAGGUGAGCAUCIAACAN	5441-5459	5441
245	CAUCUUGAAGGGUCCUCCUGC	734	GCAGGGACCCUUC AAGAUG	5519-5537	5519
246	UAUCUUGAAGGGUCCUCCUGC	735	GCAGGGACCCUUC AAGAUA	5519-5537	5519
247	NAUCUUGAAGGGUCCUCCUGC	736	GCAGGGACCCUUC AAGAUN	5519-5537	5519
248	UAUCUUGAAGGGUCCUCCUGN	737	NCAGGGACCCUUC AAGAUA	5519-5537	5519
249	NAUCUUGAAGGGUCCUCCUGN	738	NCAGGGACCCUUC AAGAUN	5519-5537	5519
250	UCGUAGUUGAGGCACAUUCU	739	AGAUGGCCUUC AACUACGA	5533-5551	5533
251	NCGUAGUUGAGGCACAUUCU	740	AGAUGGCCUUC AACUACGN	5533-5551	5533
252	UCGUAGUUGAGGCACAUUCN	741	NGAUGGCCUUC AACUACGA	5533-5551	5533

SEQ ID NO.: Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.: Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
253 NCGUAGUUAGGGCACAUCN	742 NGAUGUGCCUCAACUACGN	5533-5551	5533
254 UCGUAGUUAGGGCACAUCU	743 AGAUGUGCCUCAACUACIA	5533-5551	5533
255 NCGUAGUUAGGGCACAUCU	744 AGAUGUGCCUCAACUACIN	5533-5551	5533
256 UCGUAGUUAGGGCACAUCN	745 NGAUGUGCCUCAACUACIA	5533-5551	5533
257 NCGUAGUUAGGGCACAUCN	746 NGAUGUGCCUCAACUACIN	5533-5551	5533
258 CCUCGUAGUUAGGGCACAUCU	747 AUGUGCCUCAACUACGAGG	5535-5553	5535
259 UCUCGUAGUUAGGGCACAUCU	748 AUGUGCCUCAACUACGAGA	5535-5553	5535
260 NCUCGUAGUUAGGGCACAUCU	749 AUGUGCCUCAACUACGAGN	5535-5553	5535
261 UCUCGUAGUUAGGGCACAUCN	750 NUGUGCCUCAACUACGAGA	5535-5553	5535
262 NCUCGUAGUUAGGGCACAUCN	751 NUGUGCCUCAACUACGAGN	5535-5553	5535
263 CCUCGUAGUUAGGGCACAUCU	752 AUGUGCCUCAACUACIAGG	5535-5553	5535
264 UCUCGUAGUUAGGGCACAUCU	753 AUGUGCCUCAACUACIAGA	5535-5553	5535
265 NCUCGUAGUUAGGGCACAUCU	754 AUGUGCCUCAACUACIAGN	5535-5553	5535
266 UCUCGUAGUUAGGGCACAUCN	755 NUGUGCCUCAACUACIAGA	5535-5553	5535
267 NCUCGUAGUUAGGGCACAUCN	756 NUGUGCCUCAACUACIAGN	5535-5553	5535
268 CUUCAGGCAGGUCUCGCUG	757 CAGCGAGACCCUGCCUGAAG	1493-1511	1493
269 UUCAGGCAGGUCUCGCUG	758 CAGCGAGACCCUGCCUGAAA	1493-1511	1493
270 NUUCAGGCAGGUCUCGCUG	759 CAGCGAGACCCUGCCUGAAN	1493-1511	1493
271 UUCAGGCAGGUCUCGCUN	760 NAGCGAGACCCUGCCUGAAA	1493-1511	1493
272 NUUCAGGCAGGUCUCGCUN	761 NAGCGAGACCCUGCCUGAAN	1493-1511	1493
273 GUCUGAAGAUGGUGACGUU	762 AACGUCACCAUCUUCAGAC	1617-1635	1617
274 UUCUGAAGAUGGUGACGUU	763 AACGUCACCAUCUUCAGAA	1617-1635	1617

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
275	NUCUGAAGAUGGUGACGU	764	AACGUCACCAUCUUCAGAN	1617-1635	1617
276	UUCUGAAGAUGGUGACGUN	765	NACGUCACCAUCUUCAGAA	1617-1635	1617
277	NUCUGAAGAUGGUGACGUN	766	NACGUCACCAUCUUCAGAN	1617-1635	1617
278	GGUCUGAAGAUGGUGACGU	767	ACGUCACCAUCUUCAGACC	1618-1636	1618
279	UGUCUGAAGAUGGUGACGU	768	ACGUCACCAUCUUCAGACA	1618-1636	1618
280	NGUCUGAAGAUGGUGACGU	769	ACGUCACCAUCUUCAGACN	1618-1636	1618
281	UGUCUGAAGAUGGUGACGN	770	NCGUCACCAUCUUCAGACA	1618-1636	1618
282	NGUCUGAAGAUGGUGACGN	771	NCGUCACCAUCUUCAGACN	1618-1636	1618
283	GGUCUGAAGAUGGUGACGU	772	ACGUCACCAUCUUCAIACC	1618-1636	1618
284	UGUCUGAAGAUGGUGACGU	773	ACGUCACCAUCUUCAIACA	1618-1636	1618
285	NGUCUGAAGAUGGUGACGU	774	ACGUCACCAUCUUCAIACN	1618-1636	1618
286	UGUCUGAAGAUGGUGACGN	775	NCGUCACCAUCUUCAIACA	1618-1636	1618
287	NGUCUGAAGAUGGUGACGN	776	NCGUCACCAUCUUCAIACN	1618-1636	1618
288	CGGAAGUCAUCGGCCUGGA	777	UCCAGGCCGAUGACUUCG	1777-1795	1777
289	UGGAAGUCAUCGGCCUGGA	778	UCCAGGCCGAUGACUUGCA	1777-1795	1777
290	NGGAAGUCAUCGGCCUGGA	779	UCCAGGCCGAUGACUUCN	1777-1795	1777
291	UGGAAGUCAUCGGCCUGGN	780	NCCAGGCCGAUGACUUGCA	1777-1795	1777
292	NGGAAGUCAUCGGCCUGGN	781	NCCAGGCCGAUGACUUCN	1777-1795	1777
293	CUUGAAGGUGUUGAAGAAG	782	CUUCUUCAACACCCUUCAG	1832-1850	1832
294	UUUGAAGGUGUUGAAGAAG	783	CUUCUUCAACACCCUUCAAA	1832-1850	1832
295	NUUGAAGGUGUUGAAGAAG	784	CUUCUUCAACACCCUUCAN	1832-1850	1832
296	UUUGAAGGUGUUGAAGAAN	785	NUUCUUCAACACCCUUCAAA	1832-1850	1832

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
297	NUUGAAGGUGUUGAAGAAN	786	NUUCUUCAACACCUUCAAN	1832-1850	1832
298	UGCAGUUCGAGUAGUAGGU	787	ACCUACUACUCGAACUGCA	2001-2019	2001
299	NGCAGUUCGAGUAGUAGGU	788	ACCUACUACUCGAACUGCN	2001-2019	2001
300	UGCAGUUCGAGUAGUAGGN	789	NCCUACUACUCGAACUGCA	2001-2019	2001
301	NGCAGUUCGAGUAGUAGGN	790	NCCUACUACUCGAACUGCN	2001-2019	2001
302	UGCAGUUCGAGUAGUAGGU	791	ACCUACUACUCGAACUICA	2001-2019	2001
303	NGCAGUUCGAGUAGUAGGU	792	ACCUACUACUCGAACUICN	2001-2019	2001
304	UGCAGUUCGAGUAGUAGGN	793	NCCUACUACUCGAACUICA	2001-2019	2001
305	NGCAGUUCGAGUAGUAGGN	794	NCCUACUACUCGAACUICN	2001-2019	2001
306	CUUGGAGCAGGUGGUCCCU	795	AGGGACCACCUGCCAAG	2915-2933	2915
307	UUUGGAGCAGGUGGUCCCU	796	AGGGACCACCUGCCAAA	2915-2933	2915
308	UUUGGAGCAGGUGGUCCCU	797	AGGGACCACCUGCCAAN	2915-2933	2915
309	UUUGGAGCAGGUGGUCCCN	798	NGGGACCACCUGCCAAA	2915-2933	2915
310	UUUGGAGCAGGUGGUCCCN	799	NGGGACCACCUGCCAAN	2915-2933	2915
311	UCUUGAUGGCCUUGGAGCA	800	UGCUCCAAGGCCAUCACAA	2925-2943	2925
312	NCUUGAUGGCCUUGGAGCA	801	UGCUCCAAGGCCAUCAAAGN	2925-2943	2925
313	UCUUGAUGGCCUUGGAGCN	802	NGCUCCAAGGCCAUCACAA	2925-2943	2925
314	NCUUGAUGGCCUUGGAGCN	803	NGCUCCAAGGCCAUCAAAGN	2925-2943	2925
315	CUGUCAUCGUGGUUCCACA	804	UGUGGAACCCACGAUGACAG	610-628	610
316	UUGUCAUCGUGGUUCCACA	805	UGUGGAACCCACGAUGACAA	610-628	610
317	NUGUCAUCGUGGUUCCACA	806	UGUGGAACCCACGAUGACAN	610-628	610
318	UUGUCAUCGUGGUUCCACN	807	NGUGGAACCCACGAUGACAA	610-628	610

SEQ ID NO:.	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO:.	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
319	NUGUCAUCGUGGUUCCACN	808	NGUGGAACCCACGAUGACAN	610-628	610
320	CUGUCAUCGUGGUUCCACA	809	UGUGGAACCCACGAUIACAG	610-628	610
321	UUGUCAUCGUGGUUCCACA	810	UGUGGAACCCACGAUIACAA	610-628	610
322	NUGUCAUCGUGGUUCCACA	811	UGUGGAACCCACGAUIACAN	610-628	610
323	UUGUCAUCGUGGUUCCACN	812	NGUGGAACCCACGAUIACAA	610-628	610
324	NUGUCAUCGUGGUUCCACN	813	NGUGGAACCCACGAUIACAN	610-628	610
325	ACAGAAGCAGAGGUCUUGC	814	GCAAGACCCUCUGCUUCUGU	923-941	923
326	ACAGAAGCAGAGGUCUUGN	815	NCAAGACCCUCUGCUUCUGU	923-941	923
327	UCAGAAGCAGAGGUCUUGC	816	GCAAGACCCUCUGCUUCUGA	923-941	923
328	UCAGAAGCAGAGGUCUUGN	817	NCAAGACCCUCUGCUUCUGA	923-941	923
329	ACAGAAGCAGAGGUCUUGC	818	GCAAGACCCUCUGCUUCUIU	923-941	923
330	ACAGAAGCAGAGGUCUUGN	819	NCAAGACCCUCUGCUUCUIU	923-941	923
331	UCAGAAGCAGAGGUCUUGC	820	GCAAGACCCUCUGCUUCUIA	923-941	923
332	UCAGAAGCAGAGGUCUUGN	821	NCAAGACCCUCUGCUUCUIA	923-941	923
333	GCAGUUGGUGCAGUCUGUG	822	CACAGACUGCACC AACUGC	1277-1295	1277
334	UCAGUUGGUGCAGUCUGUG	823	CACAGACUGCACC AACUGA	1277-1295	1277
335	NCAGUUGGUGCAGUCUGUG	824	CACAGACUGCACC AACUGA	1277-1295	1277
336	UCAGUUGGUGCAGUCUGUN	825	NACAGACUGCACC AACUGN	1277-1295	1277
337	NCAGUUGGUGCAGUCUGUN	826	NACAGACUGCACC AACUGN	1277-1295	1277
338	GCAGUUGGUGCAGUCUGUG	827	CACAGACUGCACC AACUIC	1277-1295	1277
339	UCAGUUGGUGCAGUCUGUG	828	CACAGACUGCACC AACUIA	1277-1295	1277
340	NCAGUUGGUGCAGUCUGUG	829	CACAGACUGCACC AACUIA	1277-1295	1277

SEQ ID NO.: Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.: Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
341 UCAGUUGGUCAGUCUGUN	830 NACAGACUGCACCACUIN	1277-1295	1277
342 NCAGUUGGUCAGUCUGUN	831 NACAGACUGCACCACUIN	1277-1295	1277
343 GCAGUACAGUGAAGGCACU	832 AGUGCCUUCACUGUACUGC	1446-1464	1446
344 UCAGUACAGUGAAGGCACU	833 AGUGCCUUCACUGUACUGA	1446-1464	1446
345 NCAGUACAGUGAAGGCACU	834 AGUGCCUUCACUGUACUGN	1446-1464	1446
346 UCAGUACAGUGAAGGCACN	835 NGUGCCUUCACUGUACUGA	1446-1464	1446
347 NCAGUACAGUGAAGGCACN	836 NGUGCCUUCACUGUACUGN	1446-1464	1446
348 GCAGUACAGUGAAGGCACU	837 AGUGCCUUCACUGUACUIC	1446-1464	1446
349 UCAGUACAGUGAAGGCACU	838 AGUGCCUUCACUGUACUIA	1446-1464	1446
350 NCAGUACAGUGAAGGCACU	839 AGUGCCUUCACUGUACUIN	1446-1464	1446
351 UCAGUACAGUGAAGGCACN	840 NGUGCCUUCACUGUACUIA	1446-1464	1446
352 NCAGUACAGUGAAGGCACN	841 NGUGCCUUCACUGUACUIN	1446-1464	1446
353 UGCUGUUGAAGUCCCCACA	842 UGUGGGAACUUCAACAGCA	1758-1776	1758
354 NGCUGUUGAAGUCCCCACA	843 UGUGGGAACUUCAACAGCN	1758-1776	1758
355 UGCUGUUGAAGUCCCCACN	844 NGUGGGAACUUCAACAGCA	1758-1776	1758
356 NGCUGUUGAAGUCCCCACN	845 NGUGGGAACUUCAACAGCN	1758-1776	1758
357 UGCUGUUGAAGUCCCCACA	846 UGUGGGAACUUCAACAICA	1758-1776	1758
358 NGCUGUUGAAGUCCCCACA	847 UGUGGGAACUUCAACAICN	1758-1776	1758
359 UGCUGUUGAAGUCCCCACN	848 NGUGGGAACUUCAACAICA	1758-1776	1758
360 NGCUGUUGAAGUCCCCACN	849 NGUGGGAACUUCAACAICN	1758-1776	1758
361 GGAUGCUGUUGAAGUCCCC	850 GGGAAACUUAACAGCAUCC	1761-1779	1761
362 UGAUGCUGUUGAAGUCCCC	851 GGGAAACUUAACAGCAUCA	1761-1779	1761

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
363	NGAUGCUGUUGAAGUUC	852	GGGAACUUCACAGCAUC	1761-1779	1761
364	UGAUGCUGUUGAAGUUC	853	NGGAACUUCACAGCAUC	1761-1779	1761
365	NGAUGCUGUUGAAGUUC	854	NGGAACUUCACAGCAUC	1761-1779	1761
366	GGAUGCUGUUGAAGUUC	855	GGGAACUUCACAGCAUC	1761-1779	1761
367	UGAUGCUGUUGAAGUUC	856	GGGAACUUCACAGCAUC	1761-1779	1761
368	NGAUGCUGUUGAAGUUC	857	GGGAACUUCACAGCAUC	1761-1779	1761
369	UGAUGCUGUUGAAGUUC	858	NGGAACUUCACAGCAUC	1761-1779	1761
370	NGAUGCUGUUGAAGUUC	859	NGGAACUUCACAGCAUC	1761-1779	1761
371	GGGUCUUGAAGGUUGAA	860	UUCACACCCUUCAGACCC	1836-1854	1836
372	UGGUCUUGAAGGUUGAA	861	UUCACACCCUUCAGACCA	1836-1854	1836
373	NGGUCUUGAAGGUUGAA	862	UUCACACCCUUCAGACCC	1836-1854	1836
374	UGGUCUUGAAGGUUGAN	863	NUCACACCCUUCAGACCA	1836-1854	1836
375	NGGUCUUGAAGGUUGAN	864	NUCACACCCUUCAGACCC	1836-1854	1836
376	GGGUCUUGAAGGUUGAA	865	UUCACACCCUUCAGACCC	1836-1854	1836
377	UGGUCUUGAAGGUUGAA	866	UUCACACCCUUCAGACCA	1836-1854	1836
378	NGGUCUUGAAGGUUGAA	867	UUCACACCCUUCAGACCC	1836-1854	1836
379	UGGUCUUGAAGGUUGAN	868	NUCACACCCUUCAGACCA	1836-1854	1836
380	NGGUCUUGAAGGUUGAN	869	NUCACACCCUUCAGACCC	1836-1854	1836
381	AAGCUGUUCUGAUGG	870	CCAAACUACAGGACAGCUU	1867-1885	1867
382	AAGCUGUUCUGAUGU	871	NCAACUACAGGACAGCUU	1867-1885	1867
383	UAGCUGUUCUGAUGG	872	CCAAACUACAGGACAGCUU	1867-1885	1867
384	UAGCUGUUCUGAUGU	873	NCAACUACAGGACAGCUU	1867-1885	1867

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
385	NAGCUGUCCUGAUGUUGN	874	NCAACAUCAGGAACAGCUN	1867-1885	1867
386	AAGCUGUCCUGAUGUUGG	875	CCAACAUCAGGAACAICUU	1867-1885	1867
387	AAGCUGUCCUGAUGUUGN	876	NCAACAUCAGGAACAICUU	1867-1885	1867
388	UAGCUGUCCUGAUGUUGG	877	CCAACAUCAGGAACAICUN	1867-1885	1867
389	UAGCUGUCCUGAUGUUGN	878	NCAACAUCAGGAACAICUU	1867-1885	1867
390	NAGCUGUCCUGAUGUUGN	879	NCAACAUCAGGAACAICUN	1867-1885	1867
391	ACAUGCAGUUCGAGUAGUA	880	UACUACUCGAAACUGCAUGU	2004-2022	2004
392	ACAUGCAGUUCGAGUAGUN	881	NACUACUCGAAACUGCAUGU	2004-2022	2004
393	UCAUGCAGUUCGAGUAGUA	882	UACUACUCGAAACUGCAUGA	2004-2022	2004
394	UCAUGCAGUUCGAGUAGUN	883	NACUACUCGAAACUGCAUGA	2004-2022	2004
395	NCAUGCAGUUCGAGUAGUN	884	NACUACUCGAAACUGCAUGN	2004-2022	2004
396	GAAGCCAAACACUGCAGGUG	885	CACCUGCAGUUGGCUUC	2234-2252	2234
397	UAAGCCAAACACUGCAGGUG	886	CACCUGCAGUUGGCUUA	2234-2252	2234
398	NAAGCCAAACACUGCAGGUG	887	CACCUGCAGUUGGCUUN	2234-2252	2234
399	UAAGCCAAACACUGCAGGUN	888	NACCUGCAGUUGGCUUA	2234-2252	2234
400	NAAGCCAAACACUGCAGGUN	889	NACCUGCAGUUGGCUUN	2234-2252	2234
401	GAAGCCAAACACUGCAGGUG	890	CACCUGCAGUUGGCUUC	2234-2252	2234
402	UAAGCCAAACACUGCAGGUG	891	CACCUGCAGUUGGCUUA	2234-2252	2234
403	NAAGCCAAACACUGCAGGUG	892	CACCUGCAGUUGGCUUN	2234-2252	2234
404	UAAGCCAAACACUGCAGGUN	893	NACCUGCAGUUGGCUUA	2234-2252	2234
405	NAAGCCAAACACUGCAGGUN	894	NACCUGCAGUUGGCUUN	2234-2252	2234
406	CUGUAAACAGGUCUAUGUCCA	895	UGGACAUGACCUGUACAG	2536-2554	2536

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
407	UUGUACACAGGUC AUGUCCA	896	UGGACAUGACCCUGUUACAA	2536-2554	2536
408	NUGUACACAGGUC AUGUCCA	897	UGGACAUGACCCUGUUACAN	2536-2554	2536
409	UUGUACACAGGUC AUGUCCN	898	NGGACAUGACCCUGUUACAA	2536-2554	2536
410	NUGUACACAGGUC AUGUCCN	899	NGGACAUGACCCUGUUACAN	2536-2554	2536
411	CCGUUGAAGCUGU AGCUCU	900	AGAGCUACAGCUUCAAACGG	2797-2815	2797
412	UCGUUGAAGCUGU AGCUCU	901	AGAGCUACAGCUUCAAACGA	2797-2815	2797
413	NCGUUGAAGCUGU AGCUCU	902	AGAGCUACAGCUUCAAACGN	2797-2815	2797
414	UCGUUGAAGCUGU AGCUCN	903	NGAGCUACAGCUUCAAACGA	2797-2815	2797
415	NCGUUGAAGCUGU AGCUCN	904	NGAGCUACAGCUUCAAACGN	2797-2815	2797
416	CCGUUGAAGCUGU AGCUCU	905	AGAGCUACAGCUUCAAACIG	2797-2815	2797
417	UCGUUGAAGCUGU AGCUCU	906	AGAGCUACAGCUUCAAACIA	2797-2815	2797
418	NCGUUGAAGCUGU AGCUCU	907	AGAGCUACAGCUUCAAACIN	2797-2815	2797
419	UCGUUGAAGCUGU AGCUCN	908	NGAGCUACAGCUUCAAACIA	2797-2815	2797
420	NCGUUGAAGCUGU AGCUCN	909	NGAGCUACAGCUUCAAACIN	2797-2815	2797
421	CAGUACAGUGAAGGCACUG	910	CAGUGCCUUCACUGUACUG	1445-1463	1445
422	UAGUACAGUGAAGGCACUG	911	CAGUGCCUUCACUGUACUA	1445-1463	1445
423	UAGUACAGUGAAGGCACUN	912	NAGUGCCUUCACUGUACUA	1445-1463	1445
424	NAGUACAGUGAAGGCACUG	913	CAGUGCCUUCACUGUACUN	1445-1463	1445
425	NAGUACAGUGAAGGCACUN	914	NAGUGCCUUCACUGUACUN	1445-1463	1445
426	CUCGAAGCUGUUCUUGAUG	915	CAUCAGGAACAGCUUCGAG	1871-1889	1871
427	UUCGAAGCUGUUCUUGAUG	916	CAUCAGGAACAGCUUCGAA	1871-1889	1871
428	UUCGAAGCUGUUCUUGAUN	917	NAUCAGGAACAGCUUCGAA	1871-1889	1871

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
429	NUCGAAGCUGUUCUGAUG	918	CAUCAGGAACAGCUUCGAN	1871-1889	1871
430	NUCGAAGCUGUUCUGAUN	919	NAUCAGGAACAGCUUCGAN	1871-1889	1871
431	CUCGAAGCUGUUCUGAUG	920	CAUCAGGAACAGCUUCIAG	1871-1889	1871
432	UUCGAAGCUGUUCUGAUG	921	CAUCAGGAACAGCUUCIAA	1871-1889	1871
433	UUCGAAGCUGUUCUGAUN	922	NAUCAGGAACAGCUUCIAA	1871-1889	1871
434	NUCGAAGCUGUUCUGAUG	923	CAUCAGGAACAGCUUCIAN	1871-1889	1871
435	NUCGAAGCUGUUCUGAUN	924	NAUCAGGAACAGCUUCIAN	1871-1889	1871
436	UCUUGUUCAGGCAAUUCAG	925	CUGAUUUGCCUGAACAGA	4992-5010	4992
437	UCUUGUUCAGGCAAUUCAN	926	NUGAUUUGCCUGAACAGA	4992-5010	4992
438	NCUUGUUCAGGCAAUUCAG	927	CUGAUUUGCCUGAACAGN	4992-5010	4992
439	NCUUGUUCAGGCAAUUCAN	928	NUGAUUUGCCUGAACAGN	4992-5010	4992
440	UCACCAAGUGGUUGUCCU	929	AGGACAACCAUUGGUGA	6798-6816	6798
441	UCACCAAGUGGUUGUCCN	930	NGGACAACCAUUGGUGA	6798-6816	6798
442	NCACCAAGUGGUUGUCCU	931	AGGACAACCAUUGGUGN	6798-6816	6798
443	NCACCAAGUGGUUGUCCN	932	NGGACAACCAUUGGUGN	6798-6816	6798
444	UCACCAAGUGGUUGUCCU	933	AGGACAACCAUUGUGA	6798-6816	6798
445	UCACCAAGUGGUUGUCCN	934	NGGACAACCAUUGUGA	6798-6816	6798
446	NCACCAAGUGGUUGUCCU	935	AGGACAACCAUUGUGN	6798-6816	6798
447	NCACCAAGUGGUUGUCCN	936	NGGACAACCAUUGUGN	6798-6816	6798
448	GAGCAGAGGUUGUCUGGU	937	ACCAGAACAACCCUCUC	8739-8757	8739
449	UAGCAGAGGUUGUCUGGU	938	ACCAGAACAACCCUCUA	8739-8757	8739
450	UAGCAGAGGUUGUCUGGN	939	NCCAGAACAACCCUCUA	8739-8757	8739

SEQ ID NO:.	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO:.	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
451	NAGCAGAGGUUGUCUGGU	940	ACCAGAAACAACCCUCUCUN	8739-8757	8739
452	NAGCAGAGGUUGUCUGGN	941	NCCAGAAACAACCCUCUCUN	8739-8757	8739
453	GAGCAGAGGUUGUCUGGU	942	ACCAGAAACAACCCUCUCUC	8739-8757	8739
454	UAGCAGAGGUUGUCUGGU	943	ACCAGAAACAACCCUCUCUA	8739-8757	8739
455	UAGCAGAGGUUGUCUGGN	944	NCCAGAAACAACCCUCUCUA	8739-8757	8739
456	NAGCAGAGGUUGUCUGGU	945	ACCAGAAACAACCCUCUCUN	8739-8757	8739
457	NAGCAGAGGUUGUCUGGN	946	NCCAGAAACAACCCUCUCUN	8739-8757	8739
458	UAGAUUGUCUGGUUGAG	947	CUACAACCCAGCACAAUCUC	9310-9328	9310
459	UAGAUUGUCUGGUUGAG	948	CUACAACCCAGCACAAUCUA	9310-9328	9310
460	NAGAUUGUCUGGUUGAG	949	CUACAACCCAGCACAAUCUN	9310-9328	9310
461	UAGAUUGUCUGGUUGUAN	950	NUACAACCCAGCACAAUCUA	9310-9328	9310
462	NAGAUUGUCUGGUUGUAN	951	NUACAACCCAGCACAAUCUN	9310-9328	9310
463	CAGAGUUGUCUGGUUGU	952	ACAACCCAGCACAAUCUG	10206-10224	10206
464	UAGAGUUGUCUGGUUGU	953	ACAACCCAGCACAAUCUA	10206-10224	10206
465	NAGAGUUGUCUGGUUGU	954	ACAACCCAGCACAAUCUUN	10206-10224	10206
466	UAGAGUUGUCUGGUUGN	955	NCAACCCAGCACAAUCUA	10206-10224	10206
467	NAGAGUUGUCUGGUUGN	956	NCAACCCAGCACAAUCUUN	10206-10224	10206
468	CUUGUCACCAAGUGGUUG	957	CAACCAUUUGGUGACAAAG	11014-11032	11014
469	UUUGUCACCAAGUGGUUG	958	CAACCAUUUGGUGACAAA	11014-11032	11014
470	UUUGUCACCAAGUGGUUG	959	CAACCAUUUGGUGACAAAN	11014-11032	11014
471	UUUGUCACCAAGUGGUUN	960	NAACCAUUUGGUGACAAA	11014-11032	11014
472	UUUGUCACCAAGUGGUUN	961	NAACCAUUUGGUGACAAAN	11014-11032	11014

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
473	CAGAGGUUGUGUUGGUUGU	962	ACAACCAACACAAACUUCUG	11361-11379	11361
474	UAGAGGUUGUGUUGGUUGU	963	ACAACCAACACAAACUUCUA	11361-11379	11361
475	NAGAGGUUGUGUUGGUUGU	964	ACAACCAACACAAACUUCUN	11361-11379	11361
476	UAGAGGUUGUGUUGGUUGN	965	NCAACCAACACAAACUUCUA	11361-11379	11361
477	NAGAGGUUGUGUUGGUUGN	966	NCAACCAACACAAACUUCUN	11361-11379	11361
478	UCUAGUUGUAGGAGCAGAG	967	CUCUGCUCCUACAACUAGA	12965-12983	12965
479	GCUAGUUGUAGGAGCAGAG	968	CUCUGCUCCUACAACUAGC	12965-12983	12965
480	NCUAGUUGUAGGAGCAGAG	969	CUCUGCUCCUACAACUAGN	12965-12983	12965
481	UCUAGUUGUAGGAGCAGAN	970	NUCUGCUCCUACAACUAGA	12965-12983	12965
482	NCUAGUUGUAGGAGCAGAN	971	NUCUGCUCCUACAACUAGN	12965-12983	12965
483	UGGUUCAGGAACACUUCUCC	972	GGGAAGUGUUCUUGAACCA	1567-1585	1567
484	NGGUUCAGGAACACUUCUCC	973	GGGAAGUGUUCUUGAACCN	1567-1585	1567
485	UGGUUCAGGAACACUUCUCC	974	NGGAAGUGUUCUUGAACCA	1567-1585	1567
486	NGGUUCAGGAACACUUCUCC	975	NGGAAGUGUUCUUGAACCN	1567-1585	1567
487	UGGUUCAGGAACACUUCUCC	976	GGGAAGUGUUCUUGAACCA	1567-1585	1567
488	NGGUUCAGGAACACUUCUCC	977	GGGAAGUGUUCUUGAACCN	1567-1585	1567
489	UGGUUCAGGAACACUUCUCC	978	NGGAAGUGUUCUUGAACCA	1567-1585	1567
490	NGGUUCAGGAACACUUCUCC	979	NGGAAGUGUUCUUGAACCN	1567-1585	1567
491	GAUGUCGUCGAAAGUUCUCCA	980	UGGGAACUUCGACGACAUC	3155-3173	3155
492	UAUGUCGUCGAAAGUUCUCCA	981	UGGGAACUUCGACGACAUA	3155-3173	3155
493	NAUGUCGUCGAAAGUUCUCCA	982	UGGGAACUUCGACGACAUN	3155-3173	3155
494	UAUGUCGUCGAAAGUUCUCCN	983	NGGGAACUUCGACGACAUA	3155-3173	3155

SEQ ID NO.: Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.: Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
495 NAUGUCGUCGAAGUCCCN	984 NGGGAACUUCGACGACAUN	3155-3173	3155
496 GAUGUCGUCGAAGUCCCA	985 UGGGAACUUCGACIACAUC	3155-3173	3155
497 UAUGUCGUCGAAGUCCCA	986 UGGGAACUUCGACIACAUA	3155-3173	3155
498 NAUGUCGUCGAAGUCCCA	987 UGGGAACUUCGACIACAUN	3155-3173	3155
499 UAUGUCGUCGAAGUCCCN	988 NGGGAACUUCGACIACAUA	3155-3173	3155
500 NAUGUCGUCGAAGUCCCN	989 NGGGAACUUCGACIACAUN	3155-3173	3155
501 AUUCUGCCCAAGAGGAGGU	990 ACCUCCUUCUGGCAGAAAU	6777-6795	6777
502 AUUCUGCCCAAGAGGAGGN	991 NCCUCCUUCUGGCAGAAAU	6777-6795	6777
503 UUUUCUGCCCAAGAGGAGGU	992 ACCUCCUUCUGGCAGAAAU	6777-6795	6777
504 UUUUCUGCCCAAGAGGAGGN	993 NCCUCCUUCUGGCAGAAAU	6777-6795	6777
505 NUUCUGCCCAAGAGGAGGN	994 NCCUCCUUCUGGCAGAAAN	6777-6795	6777
506 AUUCUGCCCAAGAGGAGGU	995 ACCUCCUUCUGGCAGAAAU	6777-6795	6777
507 AUUCUGCCCAAGAGGAGGN	996 NCCUCCUUCUGGCAGAAAU	6777-6795	6777
508 UUUUCUGCCCAAGAGGAGGU	997 ACCUCCUUCUGGCAGAAAU	6777-6795	6777
509 UUUUCUGCCCAAGAGGAGGN	998 NCCUCCUUCUGGCAGAAAU	6777-6795	6777
510 NUUCUGCCCAAGAGGAGGN	999 NCCUCCUUCUGGCAGAAAN	6777-6795	6777
511 UGUUGUUGAAGAUUCUC	1000 GGAUUAUCUUAACAACA	15051-15069	15051
512 UGUUGUUGAAGAUUCUN	1001 NAGAUAUCUUAACAACA	15051-15069	15051
513 NGUUGUUGAAGAUUCUC	1002 GGAUUAUCUUAACAACN	15051-15069	15051
514 NGUUGUUGAAGAUUCUN	1003 NAGAUAUCUUAACAACN	15051-15069	15051
515 UGUUGUUGAAGGUUCCUU	1004 AAGGAAACCUACAACAACA	5346-5364	5346
516 NGUUGUUGAAGGUUCCUU	1005 AAGGAAACCUACAACAACN	5346-5364	5346

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
517	UGUUGUUAGGUUCCUN	1006	NAGGAAACCUACAACAACA	5346-5364	5346
518	NGUUGUUAGGUUCCUN	1007	NAGGAAACCUACAACAACN	5346-5364	5346
519	AUCUUGUCCUCAUCAAAGA	1008	UCUUUGAUGAGGACAAGAU	3694-3712	3694
520	AUCUUGUCCUCAUCAAAGN	1009	NCUUUGAUGAGGACAAGAU	3694-3712	3694
521	NUCUUGUCCUCAUCAAAGN	1010	NCUUUGAUGAGGACAAGAN	3694-3712	3694
522	UUCUUGUCCUCAUCAAAGA	1011	UCUUUGAUGAGGACAAGAA	3694-3712	3694
523	UUCUUGUCCUCAUCAAAGN	1012	NCUUUGAUGAGGACAAGAA	3694-3712	3694
524	GCAUCUUGUCCUCAUCAA	1013	UUUGAUGAGGACAAGAUGC	3696-3714	3696
525	UCAUCUUGUCCUCAUCAA	1014	UUUGAUGAGGACAAGAUGA	3696-3714	3696
526	UCAUCUUGUCCUCAUCAAN	1015	NUUGAUGAGGACAAGAUGA	3696-3714	3696
527	NCAUCUUGUCCUCAUCAA	1016	UUUGAUGAGGACAAGAUGN	3696-3714	3696
528	NCAUCUUGUCCUCAUCAAN	1017	NUUGAUGAGGACAAGAUGN	3696-3714	3696
529	GCUAGUUGUAGGAGCAGAG	1018	CUCUGUCCUACAACUAGC	6998-7016	6998
530	UCUAGUUGUAGGAGCAGAG	1019	CUCUGUCCUACAACUAGA	6998-7016	6998
531	NCUAGUUGUAGGAGCAGAG	1020	CUCUGUCCUACAACUAGN	6998-7016	6998
532	UCUAGUUGUAGGAGCAGAN	1021	NUCUGUCCUACAACUAGA	6998-7016	6998
533	NCUAGUUGUAGGAGCAGAN	1022	NUCUGUCCUACAACUAGN	6998-7016	6998
534	UAGUUGUAGAAGCAGAGGU	1023	ACCUCUGCUUACAACUA	7980-7998	7980
535	NAGUUGUAGAAGCAGAGGU	1024	ACCUCUGCUUACAACUN	7980-7998	7980
536	UAGUUGUAGAAGCAGAGGN	1025	NCCUCUGCUUACAACUA	7980-7998	7980
537	NAGUUGUAGAAGCAGAGGN	1026	NCCUCUGCUUACAACUN	7980-7998	7980
538	CAGAAGUUGUCUGGUUAU	1027	AUAACCGCACAAACUUCUG	8448-8466	8448

SEQ ID NO.:	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.:	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
539	UAGAAGUUGUCUGGUUUAU	1028	AUAACCAAGCACAACUUCUA	8448-8466	8448
540	NAGAAGUUGUCUGGUUUAU	1029	AUAACCAAGCACAACUUCUN	8448-8466	8448
541	UAGAAGUUGUCUGGUUUAU	1030	NUAACCAAGCACAACUUCUA	8448-8466	8448
542	NAGAAGUUGUCUGGUUUAU	1031	NUAACCAAGCACAACUUCUN	8448-8466	8448
543	CCAACACUGCAGGUGAUGU	1032	ACAUCACCUAGCAGUUGG	2230-2248	2230
544	UCAACACUGCAGGUGAUGU	1033	ACAUCACCUAGCAGUUGA	2230-2248	2230
545	NCAACACUGCAGGUGAUGU	1034	ACAUCACCUAGCAGUUGN	2230-2248	2230
546	UCAACACUGCAGGUGAUGN	1035	NCAUCACCUAGCAGUUGA	2230-2248	2230
547	NCAACACUGCAGGUGAUGN	1036	NCAUCACCUAGCAGUUGN	2230-2248	2230
548	CCAACACUGCAGGUGAUGU	1037	ACAUCACCUAGCAGUUGG	2230-2248	2230
549	UCAACACUGCAGGUGAUGU	1038	ACAUCACCUAGCAGUUGA	2230-2248	2230
550	NCAACACUGCAGGUGAUGU	1039	ACAUCACCUAGCAGUUGN	2230-2248	2230
551	UCAACACUGCAGGUGAUGN	1040	NCAUCACCUAGCAGUUGA	2230-2248	2230
552	NCAACACUGCAGGUGAUGN	1041	NCAUCACCUAGCAGUUGN	2230-2248	2230
553	CAUCUUGUCCUCAUCAAAG	1042	CUUUGAUGAGGACAAGAUG	3695-3713	3695
554	UAUCUUGUCCUCAUCAAAG	1043	CUUUGAUGAGGACAAGAUA	3695-3713	3695
555	NAUCUUGUCCUCAUCAAAG	1044	CUUUGAUGAGGACAAGAUN	3695-3713	3695
556	UAUCUUGUCCUCAUCAAAN	1045	NUUUGAUGAGGACAAGAUA	3695-3713	3695
557	NAUCUUGUCCUCAUCAAAN	1046	NUUUGAUGAGGACAAGAUN	3695-3713	3695
558	GUCGUGUGGUAAGACGU	1047	ACGUAUCUACCAACACGAC	3910-3928	3910
559	UUCGUGUGGUAAGACGU	1048	ACGUAUCUACCAACACGAA	3910-3928	3910
560	NUCGUGUGGUAAGACGU	1049	ACGUAUCUACCAACACGAN	3910-3928	3910

SEQ ID NO:.	Antisense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO:.	Sense Strand Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	Corresponding Positions of Identified Sequence on SEQ ID NO: 1	Targeted Gene Position
561	UUCGUGGGUAGAUGACGN	1050	NCGUCAUCUACCCACACGAA	3910-3928	3910
562	NUCGUGGGUAGAUGACGN	1051	NCGUCAUCUACCCACACGAN	3910-3928	3910
563	GUCGUGGGUAGAUGACGU	1052	ACGUCAUCUACCCACACIAC	3910-3928	3910
564	UUCGUGGGUAGAUGACGU	1053	ACGUCAUCUACCCACACIAA	3910-3928	3910
565	NUCGUGGGUAGAUGACGU	1054	ACGUCAUCUACCCACACIAN	3910-3928	3910
566	UUCGUGGGUAGAUGACGN	1055	NCGUCAUCUACCCACACIAA	3910-3928	3910
567	NUCGUGGGUAGAUGACGN	1056	NCGUCAUCUACCCACACIAN	3910-3928	3910

[0119] The MUC5AC RNAi agent sense strands and antisense strands that comprise or consist of the nucleotide sequences in Table 2 can be modified nucleotides or unmodified nucleotides. In some embodiments, the MUC5AC RNAi agents having the sense and antisense strand sequences that comprise or consist of any of the nucleotide sequences in Table 2 are all or substantially all modified nucleotides.

[0120] In some embodiments, the antisense strand of a MUC5AC RNAi agent disclosed herein comprises at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 2. In some embodiments, the sense strand of a MUC5AC RNAi agent disclosed herein comprises at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 2.

[0121] As used herein, each N listed in a sequence disclosed in Table 2 may be independently selected from any and all nucleobases (including those found on both modified and unmodified nucleotides). In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is complementary to the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is not complementary to the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is the same as the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is different from the N nucleotide at the corresponding position on the other strand.

[0122] Certain modified MUC5AC RNAi agent sense and antisense strands are provided in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 11. Certain modified MUC5AC RNAi agent antisense strands, as well as their underlying unmodified nucleobase sequences, are provided in Table 3. Certain modified MUC5AC RNAi agent sense strands, as well as their underlying unmodified nucleobase sequences, are provided in Tables 4, 5, and 6. In forming MUC5AC RNAi agents, each of the nucleotides in each of the underlying base sequences listed in Tables 3, 4, 5, 6, and 7, as well as in Table 2, above, can be a modified nucleotide.

[0123] The MUC5AC RNAi agents described herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11 can be hybridized to any antisense strand containing a sequence listed in Table 2, Table 3, or Table 11, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

[0124] In some embodiments, a MUC5AC RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 2 or Table 3.

[0125] In some embodiments, a MUC5AC RNAi agent comprises or consists of a duplex having the nucleobase sequences of the sense strand and the antisense strand of any of the sequences in Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0126] Examples of antisense strands containing modified nucleotides are provided in Table 3. Examples of sense strands containing modified nucleotides are provided in Tables 4, 5 and 6.

[0127] As used in Tables 3, 4, 5, 6, 7, and 11, the following notations are used to indicate modified nucleotides, targeting groups, and linking groups:

A	=	adenosine-3'-phosphate
C	=	cytidine-3'-phosphate
G	=	guanosine-3'-phosphate
U	=	uridine-3'-phosphate
I	=	inosine-3'-phosphate
a	=	2'-O-methyladenosine-3'-phosphate
as	=	2'-O-methyladenosine-3'-phosphorothioate
c	=	2'-O-methylcytidine-3'-phosphate
cs	=	2'-O-methylcytidine-3'-phosphorothioate
g	=	2'-O-methylguanosine-3'-phosphate
gs	=	2'-O-methylguanosine-3'-phosphorothioate
i	=	2'-O-methylinosine-3'-phosphate
is	=	2'-O-methylinosine-3'-phosphorothioate
t	=	2'-O-methyl-5-methyluridine-3'-phosphate
ts	=	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	=	2'-O-methyluridine-3'-phosphate
us	=	2'-O-methyluridine-3'-phosphorothioate
Af	=	2'-fluoroadenosine-3'-phosphate
Afs	=	2'-fluoroadenosine-3'-phosphorothioate
Cf	=	2'-fluorocytidine-3'-phosphate
Cfs	=	2'-fluorocytidine-3'-phosphorothioate
Gf	=	2'-fluoroguanosine-3'-phosphate
Gfs	=	2'-fluoroguanosine-3'-phosphorothioate
Tf	=	2'-fluoro-5'-methyluridine-3'-phosphate
Tfs	=	2'-fluoro-5'-methyluridine-3'-phosphorothioate
Uf	=	2'-fluorouridine-3'-phosphate
Ufs	=	2'-fluorouridine-3'-phosphorothioate
dT	=	2'-deoxythymidine-3'-phosphate

AUNA	=	2',3'-seco-adenosine-3'-phosphate
AUNAS	=	2',3'-seco-adenosine-3'-phosphorothioate
CUNA	=	2',3'-seco-cytidine-3'-phosphate
CUNAS	=	2',3'-seco-cytidine-3'-phosphorothioate
GUNA	=	2',3'-seco-guanosine-3'-phosphate
GUNAS	=	2',3'-seco-guanosine-3'-phosphorothioate
UUNA	=	2',3'-seco-uridine-3'-phosphate
UUNAS	=	2',3'-seco-uridine-3'-phosphorothioate
a ₂ N	=	see Table 12
a ₂ Ns	=	see Table 12
(invAb)	=	inverted abasic deoxyribonucleotide-5'-phosphate, see Table 12
(invAb)s	=	inverted abasic deoxyribonucleotide-5'-phosphorothioate, see Table 12
s	=	phosphorothioate linkage
p	=	terminal phosphate (as synthesized)
vpdN	=	vinyl phosphonate deoxyribonucleotide
cPrpa	=	5'-cyclopropyl phosphonate-2'-O-methyladenosine-3'-phosphate (see Table 12)
cPrpas	=	5'-cyclopropyl phosphonate-2'-O-methyladenosine-3'-phosphorothioate (see Table 12)
cPrpu	=	5'-cyclopropyl phosphonate-2'-O-methyluridine-3'-phosphate (see Table 12)
cPrpus	=	5'-cyclopropyl phosphonate-2'-O-methyluridine-3'-phosphorothioate (see Table 12)
(Alk-SS-C6)	=	see Table 12
(C6-SS-Alk)	=	see Table 12
(C6-SS-C6)	=	see Table 12
(6-SS-6)	=	see Table 12
(C6-SS-Alk-Me)	=	see Table 12
(NH ₂ -C6)	=	see Table 12
(TriAlk14)	=	see Table 12
(TriAlk14)s	=	see Table 12
-C6-	=	see Table 12
-C6s-	=	see Table 12
-L6-C6-	=	see Table 12
-L6-C6s-	=	see Table 12
-Alk-cyHex-	=	see Table 12
-Alk-cyHexs-	=	see Table 12
(TA14)	=	see Table 12 (structure of (TriAlk14)s after conjugation)

(TA14)s = see Table 12 (structure of (TriAlk14)s after conjugation)

[0128] As the person of ordinary skill in the art would readily understand, unless otherwise indicated by the sequence (such as, for example, by a phosphorothioate linkage “s”), when present in an oligonucleotide, the nucleotide monomers are mutually linked by 5’-3’-phosphodiester bonds. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides. Further, the person of ordinary skill in the art would readily understand that the terminal nucleotide at the 3’ end of a given oligonucleotide sequence would typically have a hydroxyl (-OH) group at the respective 3’ position of the given monomer instead of a phosphate moiety *ex vivo*. Additionally, for the embodiments disclosed herein, when viewing the respective strand 5’ → 3’, the inverted abasic residues are inserted such that the 3’ position of the deoxyribose is linked at the 3’ end of the preceding monomer on the respective strand (*see, e.g.*, Table 12). Moreover, as the person of ordinary skill would readily understand and appreciate, while the phosphorothioate chemical structures depicted herein typically show the anion on the sulfur atom, the inventions disclosed herein encompass all phosphorothioate tautomers (e.g., where the sulfur atom has a double-bond and the anion is on an oxygen atom). Unless expressly indicated otherwise herein, such understandings of the person of ordinary skill in the art are used when describing the MUC5AC RNAi agents and compositions of MUC5AC RNAi agents disclosed herein.

[0129] Certain examples of targeting groups and linking groups used with the MUC5AC RNAi agents disclosed herein are included in the chemical structures provided below in Table 12. Each sense strand and/or antisense strand disclosed herein can have any targeting groups or linking groups listed herein, as well as other targeting or linking groups, conjugated to the 5’ and/or 3’ end of the sequence.

Table 3. MUC5AC RNAi Agent Antisense Strand Sequences

AS Strand ID	Modified Antisense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10579-AS	usUfsusGfaUfgGfcCfuUfgGfaGfcAfgGfsu	1057	UUUGAUGGCCUUUGGAGCAGGU	1517
AM10581-AS	asAfsusCfuUfgAfuGfgCfcUfuGfgAfgCfsa	1058	AAUCUUUGAUGGCCUUUGGAGCA	1518
AM10583-AS	usUfsusGfaAfcUfcGfgGfgCfuGfaGfgUfsu	1059	UUUGAACUCGGGGCCUGAGGUU	1519
AM10585-AS	usGfsasUfgCfuGfcAfcUfgCfuUfcUfgGfsg	1060	UGAUGCUGCACUGCUUCUGGG	1520
AM10587-AS	usUfsasGfuCfGcfaGfaAfcAfgAfgGfgCfsa	1061	UUAGUCGCAGAACACAGAGGCA	1521
AM10589-AS	asGfsusAfgUfcGfcAfgAfaCfaGfaGfgGfsc	1062	AGUAGUCGCAGAACACAGAGGGC	1522
AM10591-AS	usUfsasGfuAfgUfcGfcAfgAfaCfaGfaGfg	1063	UUAGUAGUCGCAGAACACAGAGG	1523
AM10593-AS	usGfsusAfgUfaGfuCfGcfaGfaAfcAfgAfg	1064	UGUAGUAGUCGCAGAACACAGAG	1524
AM10595-AS	usUfsGsuUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1065	UUUGUAGUAGUCGCAGAACACAGC	1525
AM10597-AS	asUfsasGfuUfgUfaGfcAfgAfuGfgGfuGfsg	1066	AUAGUUUGUAGCAGAUUGGGUGG	1526
AM10599-AS	usUfscsCfaCfGcUfcGfaAfcCfaCfuUfuGfsc	1067	UUCACGUCGCAACACCUUUGC	1527
AM10601-AS	usAfsasGfuCfcAfcGfuCfGcfaCfcAfcUfsc	1068	UAAGUCCACGUCGAAACCACUC	1528
AM10603-AS	usGfsgsAfaGfuCfcAfcGfuCfGcfaCfcAfc	1069	UGGAAGUCCACGUCGAAACCAC	1529
AM10605-AS	usGfsgsAfaGfU _{UNA} CfcAfcGfuCfGcfaCfcAfc	1070	UGGAAGUCCACGUCGAAACCAC	1529
AM10739-AS	cPrpasAfsGsuGfuCfuUfgUfaGfuGfgAfaGfcUfsg	1071	AAGGUCUUUGUAGUGGAAAGCUG	1530
AM10741-AS	cPrpasAfsGsuGfuCfuU _{UNA} UfgUfaGfuGfgAfaGfcUfsg	1072	AAGGUCUUUGUAGUGGAAAGCUG	1530
AM10743-AS	cPrpusAfsGsuCfaGfuGfcUfgAfgCfaUfaCfuUfsc	1073	UACCAGUCGUCGAGCAUACUUC	1531
AM10744-AS	cPrpusAfsGsuCfaGfuU _{UNA} GfcUfgAfgCfaUfaCfuUfsc	1074	UACCAGUCGUCGAGCAUACUUC	1531
AM10747-AS	cPrpusUfsusGfaAfggugulUfgAfaGfaAfgGfsc	1075	UUUGAAGGUGUUUGAAGAGGC	1532
AM10764-AS	asGfsasUfgCfuGfgUfcUfuCfuUfgUfcCfsc	1076	AGAUGCUGGUCUUUCUUGUCCC	1533
AM10766-AS	usGfsusUfgAfuGfaAfgAfuGfcUfgGfuCfsc	1077	UGUUGAUGAAGAUUGCUGGUCC	1534
AM10768-AS	usUfscsUfuGfuUfcAfgGfcAfaUfaCfaGfsc	1078	UUCUUUUUCCAGGCAAAUACAGC	1535
AM10770-AS	asUfsgsUfuGfuUfgUfaGfgUfuUfcCfuUfsg	1079	AUGUUUUUUGAAGGUUUUCCUUG	1536
AM10772-AS	asUfsgsAfuGfuUfgUfuGfuAfgGfuUfuCfsc	1080	AUGAUGUUUUUGUAGGUUUUCC	1537

AM10790-AS	usUfsgsAfuGfaAfgAfuGfcUfgGfuCfuUfsc	1081	UUGAUGAAGAUGCUGGUCUUC	1538
AM10792-AS	usGfsasUfcUfgGfuAfgUfuGfuAfgCfaGfsc	1082	UGAUCUGGUAGUUGUAGCAGC	1539
AM10794-AS	usCfscsUfgAfuCfuGfgUfaGfuUfgUfaGfsc	1083	UCCUGAUCUGGUAGUUGUAGC	1540
AM10796-AS	usAfsGsUfuGfuAfgCfaGfaUfgGfgUfgGfsg	1084	UAGUUGUAGCAGAUUGGGUGGG	1541
AM10798-AS	usCfsasAfcAfcUfgGfaUfgCfgGfaUfcUfsc	1085	UCAACACUGGAUGCGGAUCUC	1542
AM10800-AS	usUfsgsUfuCfuGfuAfuGfcUfcAfcCfuCfuGfsg	1086	UUGUUGGAUGCUCACCCUCUGG	1543
AM10802-AS	usAfsusCfuUfgAfaGfgGfuCfcCfuGfcUfsg	1087	UAUCUUGAAGGGUCCUGCUG	1544
AM10804-AS	usCfsgsUfaGfuUfgAfgGfcAfcAfuCfuUfsg	1088	UCGUAGUUGAGGCACACUUG	1545
AM10806-AS	usCfsusCfuGfuUfgAfgGfcAfcAfuCfsc	1089	UCUCGUAGUUGAGGCACAUCC	1546
AM10808-AS	asAfsGsGfuCfuUfgUfaGfuGfgAfaGfcUfsg	1090	AAGGUCUUGUAGUGGAAGCUG	1530
AM10810-AS	usUfsgsCfaGfgCfaGfgUfcUfcGfcUfgUfsc	1091	UUUCAGGCAGGUCUGGCUGUC	1547
AM10812-AS	usUfscsUfgAfaGfaUfgGfuGfaCfuGfuGfsg	1092	UUCUGAAGAUGGUGACGUUGG	1548
AM10814-AS	usGfsusCfuGfaAfgAfuGfgUfgAfcGfuUfsg	1093	UGUCUGAAGAUGGUGACGUUG	1549
AM10816-AS	usGfsgsAfaGfuUfaCfaUfcGfgCfcUfgGfaUfsg	1094	UGGAAGUCAUCGGCCUGGAUG	1550
AM10818-AS	usUfsgsGfaAfgguUfgAfaGfaAfgGfsc	1095	UUUGAAGGUGUUGAAGAAAGGC	1532
AM10821-AS	usGfscsAfgUfuCfuGfuUfgAfaGfuAfgGfuUfsc	1096	UGCAGUUCGAGUAGUAGGUUC	1551
AM10823-AS	usUfsgsGfgAfgCfaGfgUfgGfuCfcCfuGfsc	1097	UUUGGAGCAGGUGGUCCUGU	1552
AM10825-AS	usCfsusUfgAfuGfgCfcUfuGfgAfgCfaGfsg	1098	UCUUGAUGGCCUUGGAGCAGG	1553
AM10827-AS	usUfsgsUfcAfuCfuUfgGfuUfcCfaCfaUfsg	1099	UUGUCAUCGUGGUUCCACAUG	1554
AM10829-AS	asCfsasGfaAfgCfaGfaGfgUfcUfuGfcCfsu	1100	ACAGAAGCAGAGGUUCCUUGCCU	1555
AM10831-AS	usCfsasGfuUfgGfuGfcAfgUfcUfgUfgGfsg	1101	UCAGUUGGUGCAGUUCUGUGGA	1556
AM10833-AS	usCfsasGfuAfcAfgUfgAfaGfgCfaCfuGfsc	1102	UCAGUACAGUAGAAAGGCACUGC	1557
AM10835-AS	usGfscsUfgUfuGfaAfgUfuCfcCfaCfaGfsc	1103	UGCUGUUGAAGUUCACACAGC	1558
AM10837-AS	usGfsasUfgCfuGfuUfgAfaGfuUfcCfcAfc	1104	UGAUGCUGUUGAAGUUCACAC	1559
AM10839-AS	usGfsgsUfcUfuGfaAfgGfuGfuUfgAfaGfsc	1105	UGGUCUUGAAGGUGUUGAAGC	1560
AM10841-AS	asAfsGsCfuGfuUfcCfuGfaUfgUfgUfgGfsg	1106	AAGCUGUUCUGAUGUUGGGG	1561
AM10843-AS	asCfsasUfgCfaGfuUfcGfaGfaUfgAfaGfsg	1107	ACAUGCAGUUCGAGUAGUAGG	1562
AM10845-AS	usAfsasGfcCfaAfcUfgCfaGfgUfgAfc	1108	UAGGCCAACACUGCAGGUGAC	1563

AM110847-AS	usUfsgsUfaAfcAfgGfuCfaUfgUfcCfaGfsc	1109	UUGUAACAGGUCAUGUCCAGC	1564
AM110849-AS	usCfsgsUfuGfaAfgCfuGfuAfgCfuCfuGfsc	1110	UCGUUGAAGCUGUAGCUCUGC	1565
AM111065-AS	usAfcscCfaGfU _{UNA} GfcUfgAfgCfaUfaCfuUfsc	1111	UACCAGUGCUGAGCAUACUUC	1531
AM111264-AS	cPrpusGfsgsAfuCfuCfaUfaGfuUfgUfaGfcAfg	1112	UGGAUCUCAUAGUUUGUAGCAG	1566
AM111266-AS	cPrpusGfsgsAfuCfuU _{JUNA} CfaUfaGfuUfgUfaGfcAfg	1113	UGGAUCUCAUAGUUUGUAGCAG	1566
AM111268-AS	cPrpusGfsgsCfaAfaCfcAfcUfuGfgUfcCfaGfsg	1114	UGUCAAAACACUUGGUCCAGG	1567
AM111271-AS	cPrpusUfsgsUfuGfuUfgAfaGfaUfgAfuCfuCfsg	1115	UUGUUUGUUGAAGAUAGAUUCG	1568
AM111272-AS	cPrpusUfsgsUfuguuagaaGfaUfgAfuucscg	1116	UUGUUUGUUGAAGAUAGAUUCG	1568
AM111275-AS	usAfcsgUfaCfaGfuGfaAfgGfcAfcUfgCfsu	1117	UAGUACAGUGAAGGCACUGCU	1569
AM111277-AS	usUfscsGfaAfgCfuGfuUfcCfuGfaUfgUfsc	1118	UUCGAAGCUGUUCUUGAUGUC	1570
AM111279-AS	usCfsusUfgUfuCfaGfgCfaAfaUfcAfgCfsc	1119	UCUUGUUUCAGGCAAAUUCAGCC	1571
AM111281-AS	usCfsasCfcAfaAfgUfgGfuUfgUfcCfuGfsg	1120	UCACCAAAGUGGUUGUCCUGG	1572
AM111283-AS	usAfcsgCfaGfaGfgUfuGfuUfcUfgGfuUfsg	1121	UAGCAGAGGUUGUUCUGGUUG	1573
AM111285-AS	usAfcsgsAfuUfgUfgCfuGfuUfgUfuAfgCfsg	1122	UAGAUUGUGCUGGUUGUAGCG	1574
AM111287-AS	usAfcsgsAfaGfuUfgUfgCfuGfgUfuGfuGfsg	1123	UAGAAGUUUGUGCUGGUUGUGG	1575
AM111289-AS	usUfsgsGfuCfaCfcAfaAfgUfgGfuUfgUfsc	1124	UUUGUCACCAAAGUGGUUGUC	1576
AM111291-AS	usAfcsgsAfgGfuUfgUfuGfgUfuGfuUfsg	1125	UAGAGGUUGUGUUGGUUGUAG	1577
AM111293-AS	usCfsusAfgUfuGfuAfgGfaGfcAfgAfgGfsu	1126	UCUAGUUUGUAGGAGCAGAGGU	1578
AM111401-AS	cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1127	UUGUAGUAGUCGCGAGAACAGC	1525
AM111403-AS	usUfsgsUfaGfuAfgUfcAfcAfgAfaCfaGfsc	1128	UUGUAGUAGUCACAGAACAGC	1579
AM111404-AS	cPrpusUfsgsUfaGfuAfgUfcAfcAfgAfaCfaGfsc	1129	UUGUAGUAGUCACAGAACAGC	1579
AM111405-AS	cPrpusUfsgsuaguagucAfcAfgAfacagsc	1130	UUGUAGUAGUCACAGAACAGC	1579
AM111462-AS	cPrpusCfsasuauguuaGfcAfcAfuugggsu	1131	UCAUAGUUUGUAGCACAUGGGU	1580
AM111464-AS	cPrpusGfsgsUfgUfuGfaAfgAfuGfaUfcUfgGfsu	1132	UGUUUGUUGAAGAUAGAUUCUGGU	1581
AM111465-AS	cPrpusGfsgsuguuagaaGfaUfcugggsu	1133	UGUUUGUUGAAGAUAGAUUCUGGU	1581
AM111467-AS	cPrpusGfsgsUfgAfaGfuUfaCfcAfcAfgAfgCfsc	1134	UGUUGAAGUUUACACAGAGCC	1582
AM111469-AS	cPrpusAfcscsUfuUfuCfaUfuCfuCfcAfcGfcUfsc	1135	UACUUUUCAUUCUCCACGCUC	1583
AM111471-AS	cPrpusAfcsgsCfaUfaCfuUfuUfcAfuUfcCfsc	1136	UAGCAUACUUUUUCAUUCUCCC	1584

AM11473-AS	cPrpusCfsasUfaCfaUfgCfaGfuUfcGfaGfaAfsG	1137	UCAUACAUGCAGUUCGAGAAG	1585
AM11475-AS	cPrpusGfsusCfaUfaCfaUfgCfaGfuUfcGfaGfsc	1138	UGUCAUAUGCAGUUCGAGC	1586
AM11477-AS	cPrpusUfsgsUfcAfuAfcAfuGfcAfgUfuCfGfAfsG	1139	UUGUCAUAUGCAGUUCGAG	1587
AM11479-AS	cPrpusUfsasGfuAfgUfcAfcAfgAfaCfaGfuGfsg	1140	UUAUGUAGUCACAGAACAGUGG	1588
AM11481-AS	cPrpusGfsusAfgUfaGfuCfaCfaGfaAfaAfgUfsg	1141	UGUAGUAGUCACAGAACAGUG	1589
AM11495-AS	cPrpusUfsgsUfaGfuAfgUfcicAfgAfaCfaGfsc	1142	UUGUAGUAGUCACAGAACAGC	1590
AM11496-AS	cPrpusUfsgsUfaGfuAfgUfcgAfgAfaCfaGfsc	1143	UUGUAGUAGUCGACAGAACAGC	1525
AM11498-AS	asCfsasUfgCfaGfuUfcGfaGfaAfgAfaGfsg	1144	ACAUGCAGUUCGAGAGAAAGG	1591
AM11499-AS	cPrpasCfsasUfgCfaGfuUfcGfaGfaAfgAfaGfsg	1145	ACAUGCAGUUCGAGAGAAAGG	1591
AM11740-AS	cPrpasUfsasGfuUfgUfaGfcAfaAfuGfgGfuGfsg	1146	AUAGUUGUAGCACAUUGGGUGG	1592
AM11741-AS	cPrpasUfsasguuagcAfcAfuGfgguugsg	1147	AUAGUUGUAGCACAUUGGGUGG	1592
AM11742-AS	cPrpusGfsgsaucucuaaGfuUfgUfagcagsg	1148	UGGAUCUCAUAGUUGUAGCAG	1566
AM11745-AS	cPrpusUfsgsuuguugaaGfaUfgAfucucsg	1149	UUGUUGUUGAAGAUUGAUCUG	1568
AM11821-AS	cPrpusGfsusAfguagucaCfaGfaAfcagugsg	1150	UGUAGUAGUCACAGAACAGUG	1589
AM11823-AS	cPrpusGfsusaguagucaCfaGfaAfcagugsg	1151	UGUAGUAGUCACAGAACAGUG	1589
AM11825-AS	cPrpusGfsusaguagucaCfaGfaAfcagusc	1152	UGUAGUAGUCACAGAACAGUC	1593
AM11971-AS	usGfsgsUfuCfaGfgAfaCfaCfuUfcCfcCfsa	1153	UGGUUCAGGAACACUUCGCCA	1594
AM11973-AS	usCfsasAfcAfcUfgCfaGfgUfgAfuGfuCfsc	1154	UCAACACUGCAGGUGAUGUCC	1595
AM11975-AS	usAfsusGfuCfGfUfcGfaAfgUfuCfcCfaCfsa	1155	UAUGUCGUCGAAAGUUCGCCA	1596
AM11977-AS	usAfsusCfuUfgUfcCfuCfaUfcAfaAfgAfsG	1156	UAUCUUGUCCUCAUCAAGAC	1597
AM11979-AS	usUfscsGfuGfuGfgUfaGfaUfgAfcGfuCfsc	1157	UUCGUGUGGUAGAUAGACGUCC	1598
AM11982-AS	asUfsusUfcUfgCfcAfaGfaGfgAfgGfuGfsc	1158	AUUUCUGCCAAGAGGAGGUGC	1599
AM11984-AS	usGfsusUfgUfuGfaAfgAfuGfaUfcUfcGfsu	1159	UGUUGUUGAAGAUGAUCUCGU	1600
AM11986-AS	usUfsgsUfuguuugaaGfaUfgAfucucsg	1160	UUGUUGUUGAAGAUGAUCUCG	1568
AM12158-AS	usGfsusUfgUfuGfuAfgGfuUfuCfcUfuGfsc	1161	UGUUGUUGAAGGUUUCCUUGC	1601
AM12159-AS	cPrpusGfsusUfgUfuGfuAfgGfuUfuCfcUfuGfsc	1162	UGUUGUUGAAGGUUUCCUUGC	1601
AM12161-AS	usGfsusuguuagGfuUfuCfcuugsg	1163	UGUUGUUGAAGGUUUCCUUGC	1601
AM12162-AS	cPrpusGfsusuguuagGfuUfuCfcuugsg	1164	UGUUGUUGAAGGUUUCCUUGC	1601

AM12163-AS	cPrpusUfscsUfuGfuUfcAfgGfcAfaAfuCfaGfsc	1165	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12165-AS	usUfscsuuguucagGfcAfaAfuucagsc	1166	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12166-AS	cPrpusUfscsuuguucagGfcAfaAfuucagsc	1167	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12167-AS	cPrpusUfscsuugU _{UNA} ucagGfcAfaAfuucagsc	1168	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12169-AS	cPrpusCfsusUfgUfuCfaGfgCfaAfaUfcAfgCfsc	1169	UCUUGUUCAGGCCAAAUCAGCC	1571
AM12171-AS	usCfsusuguucagGfcAfaAfuucagsc	1170	UCUUGUUCAGGCCAAAUCAGCC	1571
AM12172-AS	cPrpusCfsusuguucagGfcAfaAfuucagsc	1171	UCUUGUUCAGGCCAAAUCAGCC	1571
AM12173-AS	cPrpusGfsusUfgAfuGfaAfgAfuGfcUfgGfuCfsc	1172	UGUUGAUGAAGAUGCUGGUCC	1534
AM12175-AS	usGfsusugaagaagAfuGfcUfggucc	1173	UGUUGAUGAAGAUGCUGGUCC	1534
AM12176-AS	cPrpusGfsusugaagaagAfuGfcUfggucc	1174	UGUUGAUGAAGAUGCUGGUCC	1534
AM12177-AS	cPrpusGfsusugaU _{UNA} gaagAfuGfcUfggucc	1175	UGUUGAUGAAGAUGCUGGUCC	1534
AM12178-AS	cPrpusUfsgsUfugU _{UNA} ugaaGfaUfgAfuucscg	1176	UUGUUGUUGAAGAUGAUCUCG	1568
AM12180-AS	cPrpusUfsgsUfuguU _{UNA} gaaGfaUfgAfuucscg	1177	UUGUUGUUGAAGAUGAUCUCG	1568
AM12181-AS	cPrpusUfsgsUfU _{UNA} guugaaGfaUfgAfuucscg	1178	UUGUUGUUGAAGAUGAUCUCG	1568
AM12182-AS	cPrpusUfsgsiuguugaaGfaUfgAfuucscg	1179	UUGUUGUUGAAGAUGAUCUCG	1602
AM12189-AS	asUfscsUfuGfuCfcUfcAfuCfaAfaGfaUfsg	1180	AUCUUGUCCUCAUCAAAGAUG	1603
AM12191-AS	usCfsasUfcUfuGfuCfcUfcAfuCfaAfaGfsc	1181	UCAUCUUGUCCUCAUCAAAGC	1604
AM12193-AS	usCfsusAfgUfuGfuAfgGfaGfcAfgAfgAfs	1182	UCUAGUUGUAGGAGCAGAGAC	1605
AM12195-AS	usAfsGsUfuGfuAfgAfaGfcAfgAfgGfuUfsg	1183	UAGUUGUAGAAAGCAGAGGUUG	1606
AM12197-AS	usAfsGsAfaGfuUfgUfgCfuGfgUfuAfuAfs	1184	UAGAAGUUGUGCUGGUUUAUAG	1607
AM12516-AS	usUfsgsuaguagucGfcAfgAfacagsc	1185	UUGUAGUAGUCGCAGAACAGC	1525
AM12519-AS	usUfsgsuagU _{UNA} agucGfcAfgAfacagsc	1186	UUGUAGUAGUCGCAGAACAGC	1525
AM12608-AS	usUfscsuuguucagGfcAfaAfuucagsg	1187	UUCUUGUUCAGGCCAAAUCAGG	1608
AM12609-AS	usUfscsuuGfuucagGfcAfaAfuucagsc	1188	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12610-AS	usUfscsUfuguucagGfcAfaAfuucagsc	1189	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12611-AS	usUfscsuuguU _{UNA} cagGfcAfaAfuucagsc	1190	UUCUUGUUCAGGCCAAAUCAGC	1535
AM12612-AS	cPrpuUfcuuguucagGfcAfaAfuucagsc	1191	UUCUUGUUCAGGCCAAAUCAGC	1535
AM08569-AS	usGfsGsAfuCfuCfaUfaGfuUfgUfaGfcAfs	1716	UGGAUCUCAUAGUUGUAGCAG	1566

AM07104-AS	usUfsgsUfuGfuUfgAfaGfaUfgAfuCfuCfsg	1717	UUGUUUGUUUGAAGAUGAUCUCG	1568
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Table 4. MUC5AC Agent Sense Strand Sequences (Shown Without Linkers, Conjugates, or Capping Moieties)

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10578-SS-NL	ascgucucCfAfAfcicaucaaa	1192	ACCUGCUCCAAAGICCAUCAA	1609
AM10580-SS-NL	usguccaaGfCfCfcaucaagauu	1193	UGCUCAAAGGCCAUCAAGAUU	1610
AM10582-SS-NL	asaccucagCfUfCfCfagaucaaa	1194	AACCUCAGCUCGAGUUCAAA	1611
AM10584-SS-NL	cscagaagCfAfGfugcauca	1195	CCCAGAACGAGUGCAUCA	1612
AM10586-SS-NL	usgcccucGfUfUfCfCfcauca	1196	UGCCUCUGUUCUGCIACUA	1613
AM10588-SS-NL	gsccucugUfUfCfCfCfcauca	1197	GCCUCUGUUCUGCIACUA	1614
AM10590-SS-NL	cscucuguCfUfGfCfCfcauca	1198	CCUCUGUUCUGCGACUACUA	1615
AM10592-SS-NL	csucuguucUfGfCfCfcauca	1199	CUCUGUUCUGCGACUACUA	1616
AM10594-SS-NL	gscuguucGfCfGfCfcauca	1200	GCUGUUCUGCGACUACUA	1617
AM10596-SS-NL	cscaccuCfUfGfCfcauca	1201	CCACCAUCUGCUACAU	1618
AM10598-SS-NL	gscaagugGfUfUfCfCfcauca	1202	GCAAGUGGUUCGACIUGGAA	1619
AM10600-SS-NL	gsagugguUfCfCfCfCfcauca	1203	GAGUGGUUCGACGUGIACUA	1620
AM10602-SS-NL	gsugguucGfCfGfCfcauca	1204	GUGGUUCGACGUGIACUA	1621
AM10604-SS-NL	gsugguucGfCfGfCfcauca	1205	GUGGUUCGACGUGIACUA	1622
AM10738-SS-NL	csagcuuccAfCfUfCfcauca	1206	CAGCUUCCACUACAAIACCU	1623
AM10740-SS-NL	csagcuuccAfCfUfCfcauca	1207	CAGCUUCCACUACAAIACCU	1624
AM10742-SS-NL	gsa_2NaguugCfUfCfCfcauca	1208	G(A ^{2N})AGUAUGCUCAGCACUGIUA	1625
AM10745-SS-NL	gsa_2NaguugCfUfCfCfcauca	1209	G(A ^{2N})AGUAUGCUCAGCACUGIUA	1626
AM10746-SS-NL	gsccuucCfAfAfCfcauca	1210	GCCUUCUCAAACACCUUCAA	1627
AM10748-SS-NL	gsccuucCfAfAfCfcauca	1211	GCCUUCUCAAACACCUUCAA	1628
AM10749-SS-NL	gsccuucCfAfAfCfcauca	1212	GCCUUCUCAAACACCUUCAA	1629
AM10763-SS-NL	gsagacaagAfAfGfCfcauca	1213	GGGACAAGAGACCAUCA	1630

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10765-SS-NL	gsgaccagcAfUfCfuucauca	1214	GGACCAGCAUCUUAACAACA	1631
AM10767-SS-NL	gscugauuuGfCfCfugaacaagaa	1215	GCUGAUUUUGCCUGAACAAAGAA	1632
AM10769-SS-NL	csa_2NaggaaacCfUfacaacaacau	1216	C(A ^{2N})AGGAAACCUACAACAACAU	1633
AM10771-SS-NL	gsgaaacuuAfCfAfacaacaucuu	1217	GGAACCCUACAACAACAACAUCAU	1634
AM10789-SS-NL	gsa_2NagaccaGfCfAfucuucauca	1218	G(A ^{2N})AGACCAGCAUCUUAACA	1635
AM10791-SS-NL	gscugcuacAfAfCfuacciauca	1219	GCUGCUACAACUACCAUAUCA	1636
AM10793-SS-NL	gscuacaacUfAfCfagaucalga	1220	GCUACAACUACCAGAUCAIGA	1637
AM10795-SS-NL	cscacccaUfCfUfgcuacaacua	1221	CCCACCAUCUCGUACAACUA	1638
AM10797-SS-NL	gsagaucgcCfAfUfccaguiiuga	1222	GAGAUCCGCAUCCAGUIIUUGA	1639
AM10799-SS-NL	cscagagguGfAfGfcauciaacaa	1223	CCAGAGGUGAGCAUCIAACAA	1640
AM10801-SS-NL	csagcagggAfCfCfuucaagaua	1224	CAGCAGGGACCCUUAAGAUA	1641
AM10803-SS-NL	csa_2NagauguGfCfCfuaacuacia	1225	C(A ^{2N})AGAUGUGCCUACAACUACIA	1642
AM10805-SS-NL	gsgaugugcCfUfCfaacuaciaga	1226	GGAUGUGCCUACAACUACIAGA	1643
AM10807-SS-NL	csagcuuccAfCfUfacaaiacuu	1227	CAGCUUCCACUACAIAACCUU	1623
AM10809-SS-NL	gsacagcgaGfAfCfugcuugaaa	1228	GACAGCGAGACCCUGCUUGAAA	1644
AM10811-SS-NL	csaacgucAfCfCfauucuucagaa	1229	CCAACGUCACCAUCUUCAGAA	1645
AM10813-SS-NL	csa_2NacgucaCfCfAfucuuaiaca	1230	C(A ^{2N})ACGUCACCAUCUUAACA	1646
AM10815-SS-NL	csauccaggCfCfCfauagacuucca	1231	CAUCCAGGCCGGAUGACUUA	1647
AM10817-SS-NL	gscuuuuCfAfAfaccuucaaaa	1232	GCCUUCUUAACACCCUUA	1627
AM10819-SS-NL	gsa_2NaguauGfUfCfagcacuglua	1233	G(A ^{2N})AGUAUGCUCAGCACUGIUA	1625
AM10820-SS-NL	gsa_2NaccuacUfAfCfugaacuica	1234	G(A ^{2N})ACCUACUACUCGAACUICA	1648
AM10822-SS-NL	ascaggacCfAfCfugcuucaaaa	1235	ACAGGGACACCCUGCUUCAA	1649
AM10824-SS-NL	cscugcuuccAfAfGfCfuaacaaga	1236	CCUGCUCCAAGGCUAUCAAGA	1650

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10826-SS-NL	csa_2NugugaAfCfCfagauiaa	1237	C(A ^{2N})UGUGGAACACGACGUAACAA	1651
AM10828-SS-NL	asggcaagaCfCfUfcugcuuui	1238	AGGCAAGACCUCUGCUUCUIU	1652
AM10830-SS-NL	usccacagaCfUfGfaccacaui	1239	UCCACAGACUGCACCACUA	1653
AM10832-SS-NL	gscagugccUfUfCfaguguacua	1240	GCAGUGCCUUCACUGUACUIA	1654
AM10834-SS-NL	gscuguggAfCfCfuaacaica	1241	GCUGUGGGAACUUAACAICA	1655
AM10836-SS-NL	gsugggaacUfUfCfaacaica	1242	GUGGGAACUUAACAICAUA	1656
AM10838-SS-NL	gscuucaacAfCfCfuaaiaa	1243	GCUUCAACACCUUCAAIAACA	1657
AM10840-SS-NL	cscacaacAfCfCfaggaacuu	1244	CCCCAACAUACAGGAACAICU	1658
AM10842-SS-NL	cscuacuacUfCfGfacaiaugu	1245	CCUACUACUGGAACUICAUGU	1659
AM10844-SS-NL	gsucaccugCfAfGfuguigicua	1246	GUCACCCUGCAGUGUUGICUUA	1660
AM10846-SS-NL	gscuggacaUfCfAfccuguuaca	1247	GCUGGACAUGACCUGUUAACA	1661
AM10848-SS-NL	gscagagcuAfCfAfGcuuacaia	1248	GCAGAGCUACAGCUUCAACIA	1662
AM11066-SS-NL	gsa_2NaguugCfUfCfaguacugia	1249	G(A ^{2N})AGUAUGCUCAGUACUGIUA	1626
AM11263-SS-NL	csugcuacaAfCfUfagagaucca	1250	CUGCUACAACUAUGAGAUCCA	1663
AM11265-SS-NL	csugcuacaAfCfUfagauiaucca	1251	CUGCUACAACUAUGAIAUCCA	1664
AM11267-SS-NL	cscuggaccAfAfGfugguuugaca	1252	CCUGGACCAAGUGGUUUUGACA	1665
AM11269-SS-NL	cscuggaccAfAfGfugguuuiaca	1253	CCUGGACCAAGUGGUUUUIACA	1666
AM11270-SS-NL	csgagaucUfCfUfuaacaacaa	1254	CGAGAUCAUCUUAACAACAACAA	1667
AM11274-SS-NL	asgcagugCfUfUfCfaguguacua	1255	AGCAGUGCCUUCACUGUACUA	1668
AM11276-SS-NL	gsacauacGfAfAfagcuuicia	1256	GACAUCAGGAACACGCUUCIAA	1669
AM11278-SS-NL	gscugauuUfGfCfugaacaaga	1257	GGCUGAUUUUGCCUGAACACAAGA	1670
AM11280-SS-NL	cscaggacaAfCfCfacuuiiguga	1258	CCAGGACAACACCUUUIIGUGA	1671
AM11282-SS-NL	csaacacagaAfCfAfaccuicua	1259	CAACCAGAACACCUCUICUA	1672

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM11284-SS-NL	csgcuacaaCfCfAfgcacaauca	1260	CGCUAACACCAGCACAAUCUA	1673
AM11286-SS-NL	csacaaccAfGcfacaacuucua	1261	CCACAACCAGCACAAUCUUA	1674
AM11288-SS-NL	gsacaaccaCfUfUfggugacaaa	1262	GACAACCACUUUGGUGACAAA	1675
AM11290-SS-NL	csuacaaccAfCfacaacuucua	1263	CUACAACCAACACAAUCUUA	1676
AM11292-SS-NL	asccucugCfCfuaacaucaga	1264	ACCUCUGCUCCUACAACUAGA	1677
AM11400-SS-NL	gscuguucuCfCfGfacaucuaaa	1265	GCUGUUCUGCGACUACUACAA	1617
AM11402-SS-NL	gscuguucuCfUfGfacaucuaaa	1266	GCUGUUCUGUGACUACUACAA	1678
AM11463-SS-NL	asccagauCfUfCfuucaacaaca	1267	ACCAGAUCAUCUUCACAAACA	1679
AM11466-SS-NL	gsgcucuguGfGfUfaucuacaaca	1268	GGCUCUGUGGUAACUUAACA	1680
AM11468-SS-NL	gsagcguggAfGfAfaugaaaagua	1269	GAGCGUGGAGAAUGAAAAAGUA	1681
AM11470-SS-NL	gsggagaaUfGfAfaugauaugua	1270	GGGAGAAUGAAAAAGUAUGCUA	1682
AM11472-SS-NL	csuucugaaAfCfUfgcauguauga	1271	CUUCUCGAACUGCAUGUAUGA	1683
AM11474-SS-NL	gscucgaacUfGfCfauguaugaca	1272	GCUCGAACUGCAUGUAUGACA	1684
AM11476-SS-NL	csucgaacuGfCfAfuguaugacaa	1273	CUCGAACUGCAUGUAUGACAA	1685
AM11478-SS-NL	csacuguuCfUfGfugacuacuaa	1274	CCACUGUUCUGUGACUACUAA	1686
AM11480-SS-NL	csacuguuCfUfGfugacuacuaa	1275	CACUGUUCUGUGACUACUACA	1687
AM11497-SS-NL	cscuuucUfCfGfaacuicaugu	1276	CCUUUUCUCGAAACUICAUGU	1688
AM11739-SS-NL	cscaccuUfUfGfuaacaucua	1277	CCACCAUGUGCUACAACUAU	1689
AM11743-SS-NL	csugcuaCfaAfCfUfaugaiaucca	1278	CUGCUACAACUAUGAIAUCCA	1664
AM11744-SS-NL	csgagauCfaUfCfuaacaacaaca	1279	CGAGAUCAUCUUCACAAACAA	1667
AM11822-SS-NL	csacuguUfCfUfgfuaacuaca	1280	CACUGUUCUGUGACUACUACA	1687
AM11824-SS-NL	gsacuguUfCfUfgfuaacuaca	1281	GACUGUUCUGUGACUACUACA	1690
AM11970-SS-NL	usggggaagUfGfUfuccuaacca	1282	UGGGGAAGUGUUCUUAACCA	1691

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM11972-SS-NL	gsgacaucaCfcUfgcaguiuuuga	1283	GGACAUCACCCUGCAGUIIUUGA	1692
AM11974-SS-NL	usguggaaCfuUfgaciacaaua	1284	UGUGGGAACUUCGACIACAUA	1693
AM11976-SS-NL	gsucuuugaUfgAfggacaagaua	1285	GUCUUUGAUGAGGACAAAGAU	1694
AM11978-SS-NL	gsgagcucaUfcUfaccacaciaa	1286	GGACGUAUCUACCCACACIAA	1695
AM11980-SS-NL	csugcuacaAfcUfaugaiaucca	1287	CUGCUACAACUUAUGAIAUCCA	1664
AM11981-SS-NL	gscaccuccUfcUfugicagaauu	1288	GCACCUCCUUCUUGICAGAAU	1696
AM11983-SS-NL	ascgagaucaUfcUfucaacaaca	1289	ACGAGAUAUCUUCAACAACA	1697
AM11985-SS-NL	csgagaucaUfcUfucaacaaca	1290	CGAGAUAUCUUCAACAACA	1667
AM12157-SS-NL	gscaaggaaAfcCfuacaacaaca	1291	GCAAGGAAACCUACAACAACA	1698
AM12160-SS-NL	gscaaggAfaAfcCfuacaacaaca	1292	GCAAGGAAACCUACAACAACA	1698
AM12164-SS-NL	gscugauUfuGfcCfugaacaagaa	1293	GCUGAUUUUGCCUGAACCAAGAA	1632
AM12168-SS-NL	gscugauUfuGfcCfuga_2Nacaagaa	1294	GCUGAUUUUGCCUG(A ^{2M})ACAAGAA	1699
AM12170-SS-NL	gsgcugaUfuUfgCfcugaacaaga	1295	GGCUGAUUUUGCCUGAACCAAGA	1670
AM12174-SS-NL	gsgaccaGfcAfuCfucaucaaca	1296	GGACCAGCAUCUUCAUCAACA	1631
AM12179-SS-NL	csgagaucaUfcUfuca_2Nacaaca	1297	CGAGAUAUCUUC(A ^{2M})ACAACA	1700
AM12188-SS-NL	csauuuugAfuGfaggacaagau	1298	CAUCUUUGAUGAGGACAAGAU	1701
AM12190-SS-NL	gscuuugauGfAfGgacaagaua	1299	GCUUUUGAUGAGGACAAGAU	1702
AM12192-SS-NL	gsucucugcUfcCfuacaacuaga	1300	GUCUCUGCUCCUACAACUAGA	1703
AM12194-SS-NL	csaaccucuGfcUfucuaacaucua	1301	CAACCUCUGCUUCUACAACUA	1704
AM12196-SS-NL	csua_2NuaaccAfGfCfacaacuucua	1302	CU(A ^{2M})UAACCAAGCACAAACUUCUA	1705
AM12198-SS-NL	csuaaaccAfGfCfacaacuucua	1303	CUAUAACCAAGCACAAACUUCUA	1706
AM12515-SS-NL	gscuguucUgcGfaCfuacuaca	1304	GCUGUUCUGCGACUACUACAA	1617
AM12517-SS-NL	gscuguuUgcGfaCfuacuaca	1305	GCUGUUCUGCGACUACUACAA	1617

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM12518-SS-NL	gscuguuucuGfcGfacuacuacaa	1306	GCUGUUUCUGCGACUACUACAA	1617
AM12520-SS-NL	gscuguuuuuGfcGfacuacuacaa	1307	GCUGUUUUUGCGACUACUACAA	1707
AM12521-SS-NL	gscuguuucuGfcGfauuacuacaa	1308	GCUGUUCUGCGAUUACUACAA	1708
AM12522-SS-NL	gscuguuucuGfcGfacuauuacaa	1309	GCUGUUCUGCGACUUIUACAA	1709
AM12523-SS-NL	gscuguuucuGfcGfAfcuacuacaa	1310	GCUGUUCUGCGACUACUACAA	1617
AM12605-SS-NL	gscugauuuGfcCfugaacaagaa	1311	GCUGAUUUGCCUGAACAAAGAA	1632
AM12606-SS-NL	gscugauuuGfcCfuGfaacaagaa	1312	GCUGAUUUUGCCUGAACAAAGAA	1632
AM12607-SS-NL	cscugauUfuGfcCfugaacaagaa	1313	CCUGAUUUUGCCUGAACAAAGAA	1710
AM12715-SS-NL	csgagaucaUfcUfucaacaacaa	1314	CGAGAUCAUCUUCACAAACAA	1667
AM13074-SS-NL	gscugauUfuGfcCfugaacaagaa	1315	GCUGAUUUUGCCUGAACAAAGAA	1632
AM14080-SS-NL	gscuguuucuGfcGfacuacuacaa	1316	GCUGUUCUGCGACUACUACAA	1617
AM14081-SS-NL	gscugguucuGfcGfacuacuacaa	1317	GCUGGUUCUGCGACUACUACAA	1711
AM14084-SS-NL	gscuguuucuGfcGfacuacuacaa	1318	GCUGUUCUGCGACUACUACAA	1712

(A^{2N}) = 2-aminoadenine-containing nucleotide; I = hypoxanthine (inosine) nucleotide
** For the constructs in Table 4 above, a capping moiety, such as for example, (InvAb) or s(InvAb), or a conjugate is typically located at the 3' end of the modified sense strand sequence shown (see, e.g., Table 5, below).

Table 5. MUC5AC Agent Sense Strand Sequences (Shown With TriAlk14 Linker (see Table 12 for structure information)).

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10578-SS	(TriAlk14)accugcucCfAfAfgiccauacaaas(invAb)	1319	ACCUGCUCCAAGICCAUCAA	1609
AM10580-SS	(TriAlk14)ugcucaaaGfGfCfcaucaagauus(invAb)	1320	UGCUCCAAGGCCAUCAAGAUU	1610
AM10582-SS	(TriAlk14)aaccucagCfUfCfagaguucaas(invAb)	1321	AACCUCAGCUCGAGUUCAAA	1611
AM10584-SS	(TriAlk14)cccagaagCfAfGfugcaucaas(invAb)	1322	CCCAGAAGCAGUGCAUCA	1612
AM10586-SS	(TriAlk14)ugccucucGfUfUfcugciacuuaas(invAb)	1323	UGCCUCUCUGUUCUGCIACUAA	1613
AM10588-SS	(TriAlk14)gcccucugUfUfCfugicacuacuc(invAb)	1324	GCCUCUGUUCUICGACUACU	1614
AM10590-SS	(TriAlk14)ccucuguuCfUfGfagacuacuaas(invAb)	1325	CCUCUGUUCUGCGACUACUAA	1615
AM10592-SS	(TriAlk14)cucuguuucUfGfCfagacuacuaas(invAb)	1326	CUCUGUUCUGCGACUACUACA	1616
AM10594-SS	(TriAlk14)gcuguuucGfCfGfagacuacuaas(invAb)	1327	GCUGUUCUGCGACUACUACAA	1617
AM10596-SS	(TriAlk14)ccaccuauCfUfGfcauacuaas(invAb)	1328	CCACCAUCUGCUACACUAU	1618
AM10598-SS	(TriAlk14)gcaaagugGfUfUfcgaciuggaas(invAb)	1329	GCAAAGUGGUUCGACIUGGAA	1619
AM10600-SS	(TriAlk14)gagugguuCfGfAfcgugiacuuaas(invAb)	1330	GAGUGGUUCGACGUGIACUUA	1620
AM10602-SS	(TriAlk14)gugguuucGfCfGfugiacuuccas(invAb)	1331	GUGGUUCGACGUGIACUCCA	1621
AM10604-SS	(TriAlk14)gugguuucGfCfGfugiacuuccas(invAb)	1332	GUGGUUCGACGUGGACUCCA	1622
AM10738-SS	(TriAlk14)csagcuuccAfCfUfacaiaacuuas(invAb)	1333	CAGCUUCCACUACAIAACUU	1623
AM10740-SS	(TriAlk14)csagcuuccAfCfUfacaagaccuuas(invAb)	1334	CAGCUUCCACUACAAGACUU	1624
AM10742-SS	(TriAlk14)gsa_2NaguauGfUfCfagacugiuas(invAb)	1335	G(A ^{2N})AGUAUGCUCAGCACUGIUA	1625
AM10745-SS	(TriAlk14)gsa_2NaguauGfUfCfagacugiuas(invAb)	1336	G(A ^{2N})AGUAUGCUCAGACUGIUA	1626
AM10746-SS	(TriAlk14)gscuuuuCfAfAfcacuucaas(invAb)	1337	GCCUUCUUAACACCUUCAA	1627
AM10748-SS	(TriAlk14)gscuuuuCfAfAfcacuucaas(invAb)	1338	GCCUUCUUAACACCUUCAA	1628
AM10749-SS	(TriAlk14)gscuuuuCfAfAfcacuucaas(invAb)	1339	GCCUUCUUAACACCUUCAA	1629

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10763-SS	(TriAlk14)gggacaagAfAfGfaccalcaucus(invAb)	1340	GGGACAAAGAGACCAICAUCU	1630
AM10765-SS	(TriAlk14)ggaccagAfUfCfuccaucaacas(invAb)	1341	GGACCAGCAUCUUAUCAACA	1631
AM10767-SS	(TriAlk14)gcugauuuGfCfCfugaacaagaas(invAb)	1342	GCUGAUUUUGCCUGAACCAAGAA	1632
AM10769-SS	(TriAlk14)ca_2NaggaacAfCfUfacaacaacaus(invAb)	1343	C(A ^{2N})AGGAAACCUACAACAACAU	1633
AM10771-SS	(TriAlk14)ggaaaccuAfCfAfaacaacaus(invAb)	1344	GGAAACCUACAACAACAACAU	1634
AM10789-SS	(TriAlk14)ga_2NagaccaGfCfAfucuucaucaas(invAb)	1345	G(A ^{2N})AGACCAGCAUCUUAUCAAA	1635
AM10791-SS	(TriAlk14)gcugcuacAfAfCfuaccalaucaas(invAb)	1346	GCUGCUACAACUACCAIAUCA	1636
AM10793-SS	(TriAlk14)gcuacaacUfAfCfcagaucaigas(invAb)	1347	GCUACAACUACCAGAUCAIGA	1637
AM10795-SS	(TriAlk14)cccaccaUfCfUfGcuacaacuas(invAb)	1348	CCCACCAUCUGCUACAACUA	1638
AM10797-SS	(TriAlk14)gagauccgCfAfUfccaguiuuigas(invAb)	1349	GAGAUCCGCAUCCAGUIIUUGA	1639
AM10799-SS	(TriAlk14)ccagagguGfAfGfcauciaacaas(invAb)	1350	CCAGAGGUGAGCAUCIAACAA	1640
AM10801-SS	(TriAlk14)cagcaggAfCfCfuucaagaas(invAb)	1351	CAGCAGGGACCCUUAAGAUA	1641
AM10803-SS	(TriAlk14)ca_2NagauGuGfCfCfuaacuaicias(invAb)	1352	C(A ^{2N})AGAUGUGCCUCAACUACIA	1642
AM10805-SS	(TriAlk14)ggauugcCfUfCfaacuaciagas(invAb)	1353	GGAUUGGCCUCAACUACIAGA	1643
AM10807-SS	(TriAlk14)cagcuuccAfCfUfacaaiaccuus(invAb)	1354	CAGCUUCCACUACAIAACCUU	1623
AM10809-SS	(TriAlk14)gacagcgaGfAfCfcugcuugaas(invAb)	1355	GACAGCGAGACCGUCUUGAAA	1644
AM10811-SS	(TriAlk14)ccaaagucAfCfCfauccuucagaas(invAb)	1356	CCAACGUCACCAUCUUCAGAA	1645
AM10813-SS	(TriAlk14)ca_2NagcucaCfCfAfucuucaiacas(invAb)	1357	C(A ^{2N})ACGUCACCAUCUUAICA	1646
AM10815-SS	(TriAlk14)cauccaggCfCfGfagacuuccas(invAb)	1358	CAUCCAGGCGGAGUACUCCA	1647
AM10817-SS	(TriAlk14)gccuuuuCfAfAfaccuucaas(invAb)	1359	GCCUUUUAACACCCUUAACA	1627
AM10819-SS	(TriAlk14)ga_2NaguaugCfUfCfagcacugiuas(invAb)	1360	G(A ^{2N})AGUAUGCUCAGCACUGIUA	1625
AM10820-SS	(TriAlk14)ga_2NaccuacUfAfCfucgaacuicas(invAb)	1361	G(A ^{2N})ACCUACUACUCGAACUICA	1648
AM10822-SS	(TriAlk14)acagggaCfAfCfcugcuucaas(invAb)	1362	ACAGGGACCAACCGUCUUAACA	1649

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10824-SS	(TriAlk14)ccugcuccAfAfGfgcuaucaagas(invAb)	1363	CCUGCUCCAAGGCUAUCAAGA	1650
AM10826-SS	(TriAlk14)ca_2NugugaAfCfCfagauiaacas(invAb)	1364	C(A ^{2N})JUGUGGAACACAGAUACAA	1651
AM10828-SS	(TriAlk14)aggcaagaCfCfUfcugcuucuius(invAb)	1365	AGGCAAGACCUCUGCUUUCUIU	1652
AM10830-SS	(TriAlk14)uccacagaCfUfGfcaccaacuias(invAb)	1366	UCCACAGACUGCACCAACUIA	1653
AM10832-SS	(TriAlk14)gcagugccUfUfCfagugacuuias(invAb)	1367	GCAGUGCCUUCACUGUACUIA	1654
AM10834-SS	(TriAlk14)gcuguggAfAfCfucaacaicaias(invAb)	1368	GCUGUGGGAACUUAACAICA	1655
AM10836-SS	(TriAlk14)juggggaacUfUfCfaacaicaucas(invAb)	1369	GUGGGAACUUAACAICAUCA	1656
AM10838-SS	(TriAlk14)gcuucaacAfCfCfuucaaiaccas(invAb)	1370	GCUUUAACACCUUUAACAIACCA	1657
AM10840-SS	(TriAlk14)ccccacaUfCfAfGgaacaicuus(invAb)	1371	CCCCAACAUACAGGAACAICUU	1658
AM10842-SS	(TriAlk14)ccuacuacUfCfGfaacuicaugus(invAb)	1372	CCUACUACUCGGAACUICAUGU	1659
AM10844-SS	(TriAlk14)gucaccugCfAfGfuguugicuuias(invAb)	1373	GUCACCCUGCAGUGUUGICUIA	1660
AM10846-SS	(TriAlk14)gcuggacaUfGfAfccuguuacaas(invAb)	1374	GCUGGACAUGACCUGUUUACAA	1661
AM10848-SS	(TriAlk14)gcagagcuAfCfAfGcuucaacias(invAb)	1375	GCAGAGCUACAGCUUUAACIA	1662
AM11066-SS	(TriAlk14)jga_2NaguaugCfUfCfaguacuuias(invAb)	1376	G(A ^{2N})AGUAUGCUCAGUACUGIUA	1626
AM11263-SS	(TriAlk14)csugcuacaAfCfUfaugagauccas(invAb)	1377	CUGCUACAACUUAUGAGAUCCA	1663
AM11265-SS	(TriAlk14)csugcuacaAfCfUfaugaiauccas(invAb)	1378	CUGCUACAACUUAUGAIAUCCA	1664
AM11267-SS	(TriAlk14)csuggaccAfAfGfuguuugacac(invAb)	1379	CCUGGACCAAGUGGUUUUGACA	1665
AM11269-SS	(TriAlk14)csuggaccAfAfGfuguuuiacac(invAb)	1380	CCUGGACCAAGUGGUUUUIACA	1666
AM11270-SS	(TriAlk14)csagaucaUfCfUfcaacaacaas(invAb)	1381	CGAGAUCAUCUUAACAACAACA	1667
AM11274-SS	(TriAlk14)agcagugCfUfUfcacugacuuias(invAb)	1382	AGCAGUGCCUUCACUGUACUA	1668
AM11276-SS	(TriAlk14)gacaucaGfAfAfCfagcuuiciias(invAb)	1383	GACAUACAGGAACACAGCUUCIAA	1669
AM11278-SS	(TriAlk14)ggcugauUfGfCfCfagaaacaagas(invAb)	1384	GGCUGAUUUUGCCUGAACAAAGA	1670
AM11280-SS	(TriAlk14)ccaggacaAfCfCfacuuiugacac(invAb)	1385	CCAGGACAACCCACCUUUIUGUA	1671

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM11282-SS	(TriAlk14)caaccagaAfCfAfacuucuuaas(invAb)	1386	CAACCCAGAAACACCUUCUICUA	1672
AM11284-SS	(TriAlk14)cgcuacaaCfCfAfgcacaucuaas(invAb)	1387	CGCUACAACCCAGCAGCAAAUCUA	1673
AM11286-SS	(TriAlk14)ccacaaccAfGfCfacaacuuuuaas(invAb)	1388	CCACAACCCAGCAGCAACUUCUA	1674
AM11288-SS	(TriAlk14)gacaaccaCfUfUfugugacaas(invAb)	1389	GACAACCCACUUUUGGUGACAAA	1675
AM11290-SS	(TriAlk14)cuacaaccAfAfcfacaacuuuuaas(invAb)	1390	CUACAACCCAACACAAUUCUA	1676
AM11292-SS	(TriAlk14)accucugcUfcCfuaacaauagaa(invAb)	1391	ACCUCUGCUCCUACAACUAGA	1677
AM11400-SS	(TriAlk14)gscuguuucUfcGfacuacuacaas(invAb)	1392	GCUGUUUCUGCGAGUACUACAA	1617
AM11402-SS	(TriAlk14)gscuguuucUfcGfacuacuacaas(invAb)	1393	GCUGUUUCUGUGAGUACUACAA	1678
AM11463-SS	(TriAlk14)asccagauCfUfcfuaacaacaas(invAb)	1394	ACCAGAUCAUCUUCUACAACA	1679
AM11466-SS	(TriAlk14)gsgcucuguGfGfUfaucuuaacaas(invAb)	1395	GGCUCUGUGGUAAACUUCACAA	1680
AM11468-SS	(TriAlk14)gsgcugugGfGfAfaugaaagaaas(invAb)	1396	GAGCGUGGAGAAUGAAAAAGUA	1681
AM11470-SS	(TriAlk14)gsggagaaUfcAfaaaguauagaaas(invAb)	1397	GGGAGAAUGAAAAAGUAGCUA	1682
AM11472-SS	(TriAlk14)csuucuegaAfCfUfgcauguuagaaas(invAb)	1398	CUUCUCGAACUGCAUGUAGUA	1683
AM11474-SS	(TriAlk14)gscucgaacUfcCfauuguauagaaas(invAb)	1399	GCUCGAACUGCAUGUAGUAGACA	1684
AM11476-SS	(TriAlk14)csucgaacuGfCfAfauguagaaas(invAb)	1400	CUCGAACUGCAUGUAGUAGACA	1685
AM11478-SS	(TriAlk14)csacuguuCfUfcfugacuuaacaas(invAb)	1401	CCACUGUUCUGUGAGUACUAA	1686
AM11480-SS	(TriAlk14)csacuguuCfUfcfugacuuaacaas(invAb)	1402	CACUGUUCUGUGAGUACUACA	1687
AM11497-SS	(TriAlk14)csuucuuucUfcGfacaucuaugaaas(invAb)	1403	CCUUCUUCUCGAAACUICAU	1688
AM11739-SS	(TriAlk14)csacccauGfUfcfuaacaacuaas(invAb)	1404	CCACCAUGUGCUACAACUAA	1689
AM11743-SS	(TriAlk14)csugcuAfcAfcUfaugaiauccaa(invAb)	1405	CUGCUACAACUAGUAGUACU	1664
AM11744-SS	(TriAlk14)csagauCfaUfcUfucaacaacaas(invAb)	1406	CGAGAUCAUCUUCUACAACA	1667
AM11822-SS	(TriAlk14)csacuguUfcUfcUfgacuuaacaas(invAb)	1407	CACUGUUCUGUGAGUACUACA	1687
AM11824-SS	(TriAlk14)gsacuguUfcUfcUfgacuuaacaas(invAb)	1408	GACUGUUCUGUGAGUACUACA	1690

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM11970-SS	(TriAlk14)uggggaagUfGfUfuccuaaccas(invAb)	1409	UGGGGAAGUGUUCUUAACCA	1691
AM11972-SS	(TriAlk14)ggacaucaCfCfUfgcaguiugas(invAb)	1410	GGACAUCACCGCAGUIUUGA	1692
AM11974-SS	(TriAlk14)ugugggaCfUfUfgaciacaas(invAb)	1411	UGUGGGAACUUCGACIACAUA	1693
AM11976-SS	(TriAlk14)gucuuugaUfGfAfggacaagauas(invAb)	1412	GUCUUUGAUGAGGACAAAGUA	1694
AM11978-SS	(TriAlk14)ggagcucaUfCfUfaccaciaaas(invAb)	1413	GGACGUCAUCUACCACACIAA	1695
AM11980-SS	(TriAlk14)cugcuacaAfCfUfauaiauccas(invAb)	1414	CUGCUACAACUAUGAIAUCCA	1664
AM11981-SS	(TriAlk14)gcacuccUfCfUfgicagaaas(invAb)	1415	GCACCCUCCUUGICAGAAAU	1696
AM11983-SS	(TriAlk14)acgagaucaUfCfUfucaacaacac(invAb)	1416	ACGAGAUCAUCUUAACAACA	1697
AM11985-SS	(TriAlk14)cgagaucaUfCfUfucaacaacac(invAb)	1417	CGAGAUCAUCUUAACAACA	1667
AM12157-SS	(TriAlk14)gcaaggaaAfCfCfuacaacaacac(invAb)	1418	GCAAGGAAACCUACAACAACA	1698
AM12160-SS	(TriAlk14)gcaaggAfaAfCfuacaacaacac(invAb)	1419	GCAAGGAAACCUACAACAACA	1698
AM12164-SS	(TriAlk14)gcugauUfuGfcCfugaacaagaas(invAb)	1420	GCUGAUUUGCCUGAACAAAGAA	1632
AM12168-SS	(TriAlk14)gcugauUfuGfcCfuga_2Nacaagaas(invAb)	1421	GCUGAUUUGCCUG(A ^{2M})ACAAGAA	1699
AM12170-SS	(TriAlk14)ggcugaUfuUfgCfcugaacaagaas(invAb)	1422	GGCUGAUUUGCCUGAACAAAGA	1670
AM12174-SS	(TriAlk14)ggaccaGfcAfUfuCfucaucaacaas(invAb)	1423	GGACCAGCAUCUUAUCAACA	1631
AM12179-SS	(TriAlk14)csgagaucUfCfUfuca_2Nacaacaas(invAb)	1424	CGAGAUCAUCUUC(A ^{2M})ACAACAA	1700
AM12188-SS	(TriAlk14)caucuuugAfUfgfaggacaagaas(invAb)	1425	CAUCUUUGAUGAGGACAAGAU	1701
AM12190-SS	(TriAlk14)gcuuugauGfAfggacaagaugas(invAb)	1426	GCUUUUGAUGAGGACAAGAU	1702
AM12192-SS	(TriAlk14)gucucugUfCfCfuacaacuagac(invAb)	1427	GUCUCUGCCUACAACUAGA	1703
AM12194-SS	(TriAlk14)caaccucUfCfUfucuaacaacac(invAb)	1428	CAACCUUGCUUUAACAACUA	1704
AM12196-SS	(TriAlk14)cua_2NuaaccAfgCfacaacuucac(invAb)	1429	CU(A ^{2M})UAACCAAGCACAAACUUA	1705
AM12198-SS	(TriAlk14)cuaaaccAfgCfacaacuucac(invAb)	1430	CUAUAACCAAGCACAAACUUA	1706
AM12515-SS	(TriAlk14)gcuguuucUfGfcGfCfuacaacaas(invAb)	1431	GCUGUUCUGCGACUACUACAA	1617

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM12517-SS	(TriAlk14)gcuguuCfuGfcGfacuacuacaas(invAb)	1432	GCUGUUUCUGCGACUACUACAA	1617
AM12518-SS	(TriAlk14)gcuguuuGfcGfacuacuacaas(invAb)	1433	GCUGUUUCUGCGACUACUACAA	1617
AM12520-SS	(TriAlk14)gcuguuuuGfcGfacuacuacaas(invAb)	1434	GCUGUUUUUGCGACUACUACAA	1707
AM12521-SS	(TriAlk14)gcuguuuGfcGfauuacuacaas(invAb)	1435	GCUGUUUCUGCGAUUACUACAA	1708
AM12522-SS	(TriAlk14)gcuguuuGfcGfacuuuacaas(invAb)	1436	GCUGUUUCUGCGACUACUACAA	1709
AM12523-SS	(TriAlk14)gcuguuuGfcGfAfcuacuacaas(invAb)	1437	GCUGUUUCUGCGACUACUACAA	1617
AM12605-SS	(TriAlk14)gcuguuuuGfcCfugaacaagaas(invAb)	1438	GCUGAUUUUGCCUGAACAAAGAA	1632
AM12606-SS	(TriAlk14)gcuguuuuGfcCfuGfaacaagaas(invAb)	1439	GCUGAUUUUGCCUGAACAAAGAA	1632
AM12607-SS	(TriAlk14)ccugauUfuGfcCfugaacaagaas(invAb)	1440	CCUGAUUUUGCCUGAACAAAGAA	1710
AM13074-SS	(TriAlk14)gscugauUfuGfcCfugaacaagaas(invAb)	1441	GCUGAUUUUGCCUGAACAAAGAA	1632
AM14080-SS	(TriAlk14)gscuguuuGfcGfacuacuacaas(invAb)	1442	GCUGUUUCUGCGACUACUACAA	1617
AM14081-SS	(TriAlk14)gscugguuuGfcGfacuacuacaas(invAb)	1443	GCUGGUUCUGCGACUACUACAA	1711
AM14084-SS	(TriAlk14)gscguuGfcGfcGfacuacuacaas(invAb)	1444	GCUGUUCUGCGACUACUACAA	1712

(A^{2N}) = 2-aminoadenine-containing nucleotide; I = hypoxanthine (inosine) nucleotide

Table 6. Nucleotide Sequences With End Caps Shown For Certain MUC5AC RNAi Agents Tested *In Vitro*.

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10594-SS-s	(invAb)sgcuguuuGfCfGfacuaucaas(invAb)	1445	GCUGUUCUGCGACUACUACAA	1617
AM10600-SS-s	(invAb)sggaguguuCfGfAfcgugiacuua(invAb)	1446	GAGUGGUUCGACGUGIACUUA	1620
AM10765-SS-s	(invAb)sggaccagcAfUfCfucuaucacaa(invAb)	1447	GGACCAGCAUCUUCAUCAACA	1631
AM10767-SS-s	(invAb)sgcugauuuGfCfCfugaacaagaas(invAb)	1448	GCUGAUUUUCCUGAACAAAGAA	1632
AM10769-SS-s	(invAb)scsca_2NaggaacCfCfUfacaacaacaus(invAb)	1449	C(A ^{2N})AGGAAACCUACAAACAACAU	1633
AM10771-SS-s	(invAb)sggaaccuAfCfAfacaacaacaus(invAb)	1450	GGAAACCUACAAACAACAU	1634
AM10791-SS-s	(invAb)sgcugcuacAfAfCfuaacaiaucas(invAb)	1451	GCUGCUACAACUACCAIAUCA	1636
AM10793-SS-s	(invAb)sgcuacaacUfAfCfcagaucaigas(invAb)	1452	GCUACAACUACCAGAUCAIGA	1637
AM10795-SS-s	(invAb)scceccccaUfCfUfuguacaacuas(invAb)	1453	CCCACCCAUUCUGCUACAACUA	1638
AM10797-SS-s	(invAb)sgagauccgCfAfUfcaaguiugas(invAb)	1454	GAGAUCCGCAUCCAGUIUUGA	1639
AM10799-SS-s	(invAb)scagagguGfAfGfcaucaiaacaas(invAb)	1455	CCAGAGGUGAGCAUCIAACAA	1640
AM10801-SS-s	(invAb)scagcaggAfCfCfcaucaagauas(invAb)	1456	CAGCAGGACCCUUCAAAGUA	1641
AM10803-SS-s	(invAb)scsca_2NagauguGfCfCfcaucaiaucas(invAb)	1457	C(A ^{2N})AGAUGUGCCUCAAACUACIA	1642
AM10813-SS-s	(invAb)scsca_2NacgucaCfCfAfucuaiaucas(invAb)	1458	C(A ^{2N})ACGUCACCAUCUUCUACIACA	1646
AM10820-SS-s	(invAb)sga_2NaccuacUfAfCfugaacuaucas(invAb)	1459	G(A ^{2N})ACCUACUACUCGAAACUICA	1648
AM10826-SS-s	(invAb)scsca_2NuguggaAfCfCfagauiacaas(invAb)	1460	C(A ^{2N})UGUGGAACCCAGAUACAA	1651
AM10828-SS-s	(invAb)sgagcaagaCfCfUfugcuuuius(invAb)	1461	AGGCAAGACCCUCUGCUUCUIU	1652
AM10832-SS-s	(invAb)sgcagugccUfUfCfaguguaucias(invAb)	1462	GCAGUGCCUUCACUGUACUIA	1654
AM10836-SS-s	(invAb)sguggggaacUfUfCfacaiaucaucas(invAb)	1463	GUGGGAACUUCACAICAUCA	1656
AM10840-SS-s	(invAb)scceccaacUfCfAfaggaacaicuius(invAb)	1464	CCCCAACAUACAGGAACAICUU	1658
AM10842-SS-s	(invAb)scuacuacUfCfGfcaucaicangus(invAb)	1465	CCUACUACUCGAAACUICAUUG	1659
AM10844-SS-s	(invAb)sguaccugCfAfGfugugiucaas(invAb)	1466	GUCACCCUGCAGUGUUGICUUA	1660

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3') (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO.
AM10846-SS-s	(invAb)sgcuggacaUfGfAfccuguuacaas(invAb)	1467	GCUGGACAUGACCCUGUUACAA	1661
AM10848-SS-s	(invAb)sgcagagcuAfCfAfgcucaacias(invAb)	1468	GCAGAGCUACAGCUUCAACIA	1662
AM11274-SS-s	(invAb)sagcagugcCfUfUfcauguaucas(invAb)	1469	AGCAGUGCCUUCACUGUACUA	1668
AM11276-SS-s	(invAb)sgacaucagGfAfAfcaguciaas(invAb)	1470	GACAUCAGGAACAGCUUCIAA	1669
AM11278-SS-s	(invAb)sggcuganuUfGfCfcgacaagaa(invAb)	1471	GGCUGAUUUGCCUGAACAAAGA	1670
AM11280-SS-s	(invAb)scaggacaAfCfCfcauuuigugas(invAb)	1472	CCAGGACAACCCACUUUIGUGA	1671
AM11286-SS-s	(invAb)scacaaccAfGfCfacaacuucuaas(invAb)	1473	CCACAACCAAGCACAAACUUUCUA	1674
AM11288-SS-s	(invAb)sgacaaccaCfUfUfuggugacaas(invAb)	1474	GACAACCAACUUUGGUGACAAA	1675
AM11292-SS-s	(invAb)saccuugcUfCfCfuacaacuagaa(invAb)	1475	ACCUCUGCUCCUACCAACUAGA	1677
AM11978-SS-s	(invAb)sggacgucaUfCfUfaccacaciaas(invAb)	1476	GGACGUCAUUCUACCCACACIAA	1695
AM11980-SS-s	(invAb)scugcuacaAfCfUfauagaiauccas(invAb)	1477	CUGCUACAACUAUGAIAUCCA	1664
AM11983-SS-s	(invAb)sacgagaucaUfCfUfuaacaacaas(invAb)	1478	ACGAGAUCAUCUUCUACAACA	1697
AM11985-SS-s	(invAb)scgagaucUfCfUfuaacaacaas(invAb)	1479	CGAGAUCAUCUUCUACAACA	1667
AM12164-SS-s	(invAb)sgcugauUfUfGfCfugaacaagaas(invAb)	1480	GCUGAUUUGCCUGAACAAAGAA	1632
AM12168-SS-s	(invAb)sgcugauUfUfGfCfuga_2Nacagaas(invAb)	1481	GCUGAUUUGCCUG(A ^{2N})ACAAGAA	1699
AM12170-SS-s	(invAb)sggcugaUfUfGfCfcgacaagaa(invAb)	1482	GGCUGAUUUGCCUGAACAAAGA	1670

(A^{2N}) = 2-aminoadenine-containing nucleotide; I = hypoxanthine (inosine) nucleotide

Table 7. MUC5AC Agent Sense Strand Sequences (Shown with Targeting Ligand Conjugate. The structure of $\alpha\text{v}\beta 6$ -SM6.1 is shown in Table 12, and the structure of Tri-SM6.1- $\alpha\text{v}\beta 6$ -(TA14) is shown in FIG. 1.)

Strand ID	Modified Sense Strand (5' $\rightarrow$ 3')	SEQ ID NO.	Corresponding Sense Strand AM Number Without Linker or Conjugate (See Table 4)
CS000387	Tri-SM6.1-avb6-(TA14)gsa_2NaguauGfUcfaguacugiuas(invAb)	1483	AM10745-SS
CS000517	Tri-SM6.1-avb6-(TA14)asccauguGfCfUfacaauaugas(invAb)	1484	AM09492-SS
CS000519	Tri-SM6.1-avb6-(TA14)cscauacagCfAfGfuacaguuuacac(invAb)	1485	AM09657-SS
CS000521	Tri-SM6.1-avb6-(TA14)csugcuacaAfCfUfauagagauccas(invAb)	1486	AM11263-SS
CS000523	Tri-SM6.1-avb6-(TA14)csugcuacaAfCfUfauagaiauccas(invAb)	1487	AM11265-SS
CS000525	Tri-SM6.1-avb6-(TA14)csuggagaccAfAfGfugguuuugacac(invAb)	1488	AM11267-SS
CS000527	Tri-SM6.1-avb6-(TA14)csuggagaccAfAfGfugguuuiacac(invAb)	1489	AM11269-SS
CS000528	Tri-SM6.1-avb6-(TA14)csugagaucaUfCfUfuaacaacaas(invAb)	1490	AM11270-SS
CS000578	Tri-SM6.1-avb6-(TA14)gscuguuucGfCfGfacuacuacaas(invAb)	1491	AM11400-SS
CS000583	Tri-SM6.1-avb6-(TA14)gscuguuucGfUfGfacuacuacaas(invAb)	1492	AM11402-SS
CS000608	Tri-SM6.1-avb6-(TA14)asccagauCfUfCfuaacaacaas(invAb)	1493	AM11463-SS
CS000612	Tri-SM6.1-avb6-(TA14)gsgcucugGfGfUfaucuacaas(invAb)	1494	AM11466-SS
CS000614	Tri-SM6.1-avb6-(TA14)gsagcgaggAfGfAfaugaaaaguas(invAb)	1495	AM11468-SS
CS000616	Tri-SM6.1-avb6-(TA14)gsggagaaUfGfAfaugauugcuas(invAb)	1496	AM11470-SS
CS000618	Tri-SM6.1-avb6-(TA14)csuucucgaAfCfUfcaugauugcuas(invAb)	1497	AM11472-SS
CS000620	Tri-SM6.1-avb6-(TA14)gscucgaacUfGfCfaugauugacac(invAb)	1498	AM11474-SS
CS000622	Tri-SM6.1-avb6-(TA14)csugagacuGfCfAfaugauagacaas(invAb)	1499	AM11476-SS

Strand ID	Modified Sense Strand (5' → 3')	SEQ ID NO.	Corresponding Sense Strand AM Number Without Linker or Conjugate (See Table 4)
CS000624	Tri-SM6.1-avb6-(TA14)cscacguuUfGfugacuacuaas(invAb)	1500	AM11478-SS
CS000626	Tri-SM6.1-avb6-(TA14)csacuguuUfGfugacuacuaas(invAb)	1501	AM11480-SS
CS000665	Tri-SM6.1-avb6-(TA14)csuuuUfCfGfaacuicaugus(invAb)	1502	AM11497-SS
CS001001	Tri-SM6.1-avb6-(TA14)csagcuuccAfCfUfacaalaccuus(invAb)	1503	AM10738-SS
CS001003	Tri-SM6.1-avb6-(TA14)csagcuuccAfCfUfacaagaccuus(invAb)	1504	AM10740-SS
CS001005	Tri-SM6.1-avb6-(TA14)gsa_2NaguugCfUfCfagcacugiuaas(invAb)	1505	AM10742-SS
CS001007	Tri-SM6.1-avb6-(TA14)gscuuuuCfAfaccuucaaaas(invAb)	1506	AM10746-SS
CS001009	Tri-SM6.1-avb6-(TA14)gscuuuuCfAfaccuucaaaas(invAb)	1507	AM10748-SS
CS001010	Tri-SM6.1-avb6-(TA14)gscuuuuCfAfaccuucaaaas(invAb)	1508	AM10749-SS
CS001036	Tri-SM6.1-avb6-(TA14)csaccuuGfUfGfuaacuaauas(invAb)	1509	AM11739-SS
CS001040	Tri-SM6.1-avb6-(TA14)csugcuCfAfCfUfauaiauaucas(invAb)	1510	AM11743-SS
CS001041	Tri-SM6.1-avb6-(TA14)csagauCfUfCfUfuaacuaacaaas(invAb)	1511	AM11744-SS
CS001401	Tri-SM6.1-avb6-(TA14)csagauCfUfCfUfua_2Nacaacaaas(invAb)	1512	AM12179-SS
CS001644	Tri-SM6.1-avb6-(TA14)gscugauUfUfCfCfugaacaagaas(invAb)	1513	AM13074-SS
CS002194	Tri-SM6.1-avb6-(TA14)gscuguuCfCfGfuaacuacaa(invAb)	1514	AM14080-SS
CS002195	Tri-SM6.1-avb6-(TA14)gscuguuCfCfGfuaacuacaa(invAb)	1515	AM14081-SS
CS002196	Tri-SM6.1-avb6-(TA14)gscuguuCfCfGfuaacuacaa(invAb)	1516	AM14084-SS

[0130] The MUC5AC RNAi agents disclosed herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 2, Table 4, Table 5, Table 6, or Table 7 can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

[0131] As shown in Table 5 above, certain of the example MUC5AC RNAi agent nucleotide sequences are shown to further include reactive linking groups at one or both of the 5' terminal end and the 3' terminal end of the sense strand. For example, many of the MUC5AC RNAi agent sense strand sequences shown in Table 5 above have a (TriAlk14) linking group at the 5' end of the nucleotide sequence. Other linking groups, such as an (NH₂-C6) linking group or a (6-SS-6) or (C6-SS-C6) linking group, may be present as well or alternatively in certain embodiments. Such reactive linking groups are positioned to facilitate the linking of targeting ligands, targeting groups, and/or PK/PD modulators to the MUC5AC RNAi agents disclosed herein. Linking or conjugation reactions are well known in the art and provide for formation of covalent linkages between two molecules or reactants. Suitable conjugation reactions for use in the scope of the inventions herein include, but are not limited to, amide coupling reaction, Michael addition reaction, hydrazone formation reaction, inverse-demand Diels-Alder cycloaddition reaction, oxime ligation, and Copper (I)- catalyzed or strain-promoted azide-alkyne cycloaddition reaction.

[0132] In some embodiments, targeting ligands, such as the integrin targeting ligands shown in the examples and figures disclosed herein, can be synthesized as activated esters, such as tetrafluorophenyl (TFP) esters, which can be displaced by a reactive amino group (e.g., NH₂-C₆) to attach the targeting ligand to the MUC5AC RNAi agents disclosed herein. In some embodiments, targeting ligands are synthesized as azides, which can be conjugated to a propargyl (e.g., TriAlk14) or DBCO group, for example, via Copper (I)- catalyzed or strain-promoted azide-alkyne cycloaddition reaction.

[0133] Additionally, the nucleotide sequences can be synthesized with a dT nucleotide at the 3' terminal end of the sense strand, followed by (3' → 5') a linker (e.g., C6-SS-C6). The linker can, in some embodiments, facilitate the linkage to additional components, such as, for example, a PK/PD modulator or one or more targeting ligands. The disulfide bond of C6-SS-C6 can then be reduced, removing the dT from the molecule, which can then facilitate the conjugation of the desired PK/PD modulator. The terminal dT nucleotide would therefore not be a part of the fully conjugated construct.

[0134] In some embodiments, the antisense strand of a MUC5AC RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 3 or Table 11. In some embodiments, the sense strand of a MUC5AC RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 4, Table 5, Table 6, Table 7, or Table 11.

[0135] In some embodiments, a MUC5AC RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 2 or Table 3. In some embodiments, a MUC5AC RNAi agent antisense strand comprises the sequence of nucleotides (from 5' end → 3' end) 1-17, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, 2-21, 1-22, 2-22, 1-23, 2-23, 1-24, or 2-24 of any of the sequences in Table 2, Table 3, or Table 11. In certain embodiments, a MUC5AC RNAi agent antisense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 3 or Table 11.

[0136] In some embodiments, a MUC5AC RNAi agent sense strand comprises the nucleotide sequence of any of the sequences in Table 2 or Table 4. In some embodiments, a MUC5AC RNAi agent sense strand comprises the sequence of nucleotides (from 5' end → 3' end) 1-17, 2-17, 3-17, 4-17, 1-18, 2-18, 3-18, 4-18, 1-19, 2-19, 3-19, 4-19, 1-20, 2-20, 3-20, 4-20, 1-21, 2-21, 3-21, 4-21, 1-22, 2-22, 3-22, 4-22, 1-23, 2-23, 3-23, 4-23, 1-24, 2-24, 3-24, or 4-24, of any of the sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11. In certain embodiments, a MUC5AC RNAi agent sense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 3 or Table 11.

[0137] For the RNAi agents disclosed herein, the nucleotide at position 1 of the antisense strand (from 5' end → 3' end) can be perfectly complementary to a MUC5AC gene, or can be non-complementary to a MUC5AC gene. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5' end → 3' end) is a U, A, or dT (or a modified version of U, A or dT). In some embodiments, the nucleotide at position 1 of the antisense strand (from 5' end → 3' end) forms an A:U or U:A base pair with the sense strand.

[0138] In some embodiments, a MUC5AC RNAi agent antisense strand comprises the sequence of nucleotides (from 5' end → 3' end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2, Table 3, or Table 11. In some embodiments, a MUC5AC RNAi sense strand comprises the sequence of nucleotides (from 5' end → 3' end) 1-17 or 1-18 of any of the sense strand sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0139] In some embodiments, a MUC5AC RNAi agent includes (i) an antisense strand comprising the sequence of nucleotides (from 5' end → 3' end) 2-18 or 2-19 of any of the

antisense strand sequences in Table 2, Table 3, or Table 11, and (ii) a sense strand comprising the sequence of nucleotides (from 5' end → 3' end) 1-17 or 1-18 of any of the sense strand sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0140] A sense strand containing a sequence listed in Table 2 or Table 4 can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3 provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence. In some embodiments, the MUC5AC RNAi agent has a sense strand consisting of the modified sequence of any of the modified sequences in Table 4, Table 5, Table 6, Table 7, or Table 11, and an antisense strand consisting of the modified sequence of any of the modified sequences in Table 3 or Table 11. Certain representative sequence pairings are exemplified by the Duplex ID Nos. shown in Tables 8A, 8B, 8C, 9, 10A and 10B.

[0141] In some embodiments, a MUC5AC RNAi agent comprises, consists of, or consists essentially of a duplex represented by any one of the Duplex ID Nos. presented herein. In some embodiments, a MUC5AC RNAi agent consists of any of the Duplex ID Nos. presented herein. In some embodiments, a MUC5AC RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the Duplex ID Nos. presented herein. In some embodiments, a MUC5AC RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the Duplex ID Nos. presented herein and a targeting group, linking group, and/or other non-nucleotide group wherein the targeting group, linking group, and/or other non-nucleotide group is covalently linked (i.e., conjugated) to the sense strand or the antisense strand. In some embodiments, a MUC5AC RNAi agent includes the sense strand and antisense strand modified nucleotide sequences of any of the Duplex ID Nos. presented herein. In some embodiments, a MUC5AC RNAi agent comprises the sense strand and antisense strand modified nucleotide sequences of any of the Duplex ID Nos. presented herein and a targeting group, linking group, and/or other non-nucleotide group, wherein the targeting group, linking group, and/or other non-nucleotide group is covalently linked to the sense strand or the antisense strand.

[0142] In some embodiments, a MUC5AC RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Tables 2, 8A, 8B, 8C, 9, 10A, 10B, or 11, and comprises a targeting group. In some embodiments, a MUC5AC RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Tables 2, 8A, 8B, 8C, 9, 10A, 10B, or 11, and comprises one or more $\alpha\text{v}\beta 6$ integrin targeting ligands.

[0143] In some embodiments, a MUC5AC RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Tables 2, 8A, 8B, 8C, 9, 10A, 10B, or 11, and comprises a targeting group that is an integrin targeting ligand. In some embodiments, a MUC5AC RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Tables 2, 8A, 8B, 8C, 9, 10A, 10B, or 11, and comprises one or more $\alpha v \beta 6$ integrin targeting ligands or clusters of $\alpha v \beta 6$ integrin targeting ligands (e.g., a tridentate $\alpha v \beta 6$ integrin targeting ligand).

[0144] In some embodiments, a MUC5AC RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences of any of the antisense strand/sense strand duplexes of Tables 8A, 8B, 8C, 9, 10A, 10B, and 11.

[0145] In some embodiments, a MUC5AC RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequences of any of the antisense strand/sense strand duplexes of Tables 8A, 8B, 8C, 9, 10A, 10B, and 11, and comprises an integrin targeting ligand.

[0146] In some embodiments, a MUC5AC RNAi agent comprises, consists of, or consists essentially of any of the duplexes of Tables 8A, 8B, 8C, 9, 10A, 10B, and 11.

[0147] **Table 8A.** MUC5AC RNAi Agent Duplexes with Corresponding Sense and Antisense Strand ID Numbers and Sequence ID numbers for the modified and unmodified nucleotide sequences. (Shown without Linking Agents or Conjugates)

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07626	AM10579-AS	1057	1517	AM10578-SS-NL	1192	1609
AD07627	AM10581-AS	1058	1518	AM10580-SS-NL	1193	1610
AD07628	AM10583-AS	1059	1519	AM10582-SS-NL	1194	1611
AD07629	AM10585-AS	1060	1520	AM10584-SS-NL	1195	1612
AD07630	AM10587-AS	1061	1521	AM10586-SS-NL	1196	1613
AD07631	AM10589-AS	1062	1522	AM10588-SS-NL	1197	1614
AD07632	AM10591-AS	1063	1523	AM10590-SS-NL	1198	1615
AD07633	AM10593-AS	1064	1524	AM10592-SS-NL	1199	1616
AD07634	AM10595-AS	1065	1525	AM10594-SS-NL	1200	1617
AD07635	AM10597-AS	1066	1526	AM10596-SS-NL	1201	1618
AD07636	AM10599-AS	1067	1527	AM10598-SS-NL	1202	1619
AD07637	AM10601-AS	1068	1528	AM10600-SS-NL	1203	1620

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07638	AM10603-AS	1069	1529	AM10602-SS-NL	1204	1621
AD07639	AM10605-AS	1070	1529	AM10604-SS-NL	1205	1622
AD07716	AM10739-AS	1071	1530	AM10738-SS-NL	1206	1623
AD07717	AM10741-AS	1072	1530	AM10740-SS-NL	1207	1624
AD07718	AM10743-AS	1073	1531	AM10742-SS-NL	1208	1625
AD07719	AM10744-AS	1074	1531	AM10742-SS-NL	1208	1625
AD07720	AM10743-AS	1073	1531	AM10745-SS-NL	1209	1626
AD07721	AM10747-AS	1075	1532	AM10746-SS-NL	1210	1627
AD07722	AM10747-AS	1075	1532	AM10748-SS-NL	1211	1628
AD07723	AM10747-AS	1075	1532	AM10749-SS-NL	1212	1629
AD07731	AM10764-AS	1076	1533	AM10763-SS-NL	1213	1630
AD07732	AM10766-AS	1077	1534	AM10765-SS-NL	1214	1631
AD07733	AM10768-AS	1078	1535	AM10767-SS-NL	1215	1632
AD07734	AM10770-AS	1079	1536	AM10769-SS-NL	1216	1633
AD07735	AM10772-AS	1080	1537	AM10771-SS-NL	1217	1634
AD07744	AM10790-AS	1081	1538	AM10789-SS-NL	1218	1635
AD07745	AM10792-AS	1082	1539	AM10791-SS-NL	1219	1636
AD07746	AM10794-AS	1083	1540	AM10793-SS-NL	1220	1637
AD07747	AM10796-AS	1084	1541	AM10795-SS-NL	1221	1638
AD07748	AM10798-AS	1085	1542	AM10797-SS-NL	1222	1639
AD07749	AM10800-AS	1086	1543	AM10799-SS-NL	1223	1640
AD07750	AM10802-AS	1087	1544	AM10801-SS-NL	1224	1641
AD07751	AM10804-AS	1088	1545	AM10803-SS-NL	1225	1642
AD07752	AM10806-AS	1089	1546	AM10805-SS-NL	1226	1643
AD07753	AM10808-AS	1090	1530	AM10807-SS-NL	1227	1623
AD07754	AM10810-AS	1091	1547	AM10809-SS-NL	1228	1644
AD07755	AM10812-AS	1092	1548	AM10811-SS-NL	1229	1645
AD07756	AM10814-AS	1093	1549	AM10813-SS-NL	1230	1646
AD07757	AM10816-AS	1094	1550	AM10815-SS-NL	1231	1647
AD07758	AM10818-AS	1095	1532	AM10817-SS-NL	1232	1627
AD07760	AM10821-AS	1096	1551	AM10820-SS-NL	1234	1648
AD07761	AM10823-AS	1097	1552	AM10822-SS-NL	1235	1649
AD07762	AM10825-AS	1098	1553	AM10824-SS-NL	1236	1650
AD07763	AM10827-AS	1099	1554	AM10826-SS-NL	1237	1651
AD07764	AM10829-AS	1100	1555	AM10828-SS-NL	1238	1652
AD07765	AM10831-AS	1101	1556	AM10830-SS-NL	1239	1653
AD07766	AM10833-AS	1102	1557	AM10832-SS-NL	1240	1654
AD07767	AM10835-AS	1103	1558	AM10834-SS-NL	1241	1655
AD07768	AM10837-AS	1104	1559	AM10836-SS-NL	1242	1656
AD07769	AM10839-AS	1105	1560	AM10838-SS-NL	1243	1657

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07770	AM10841-AS	1106	1561	AM10840-SS-NL	1244	1658
AD07771	AM10843-AS	1107	1562	AM10842-SS-NL	1245	1659
AD07772	AM10845-AS	1108	1563	AM10844-SS-NL	1246	1660
AD07773	AM10847-AS	1109	1564	AM10846-SS-NL	1247	1661
AD07774	AM10849-AS	1110	1565	AM10848-SS-NL	1248	1662
AD07941	AM11065-AS	1111	1531	AM10819-SS-NL	1233	1625
AD08083	AM11264-AS	1112	1566	AM11263-SS-NL	1250	1663
AD08084	AM11264-AS	1112	1566	AM11265-SS-NL	1251	1664
AD08085	AM11266-AS	1113	1566	AM11263-SS-NL	1250	1663
AD08086	AM11268-AS	1114	1567	AM11267-SS-NL	1252	1665
AD08087	AM11268-AS	1114	1567	AM11269-SS-NL	1253	1666
AD08088	AM11271-AS	1115	1568	AM11270-SS-NL	1254	1667
AD08089	AM11272-AS	1116	1568	AM11270-SS-NL	1254	1667
AD08094	AM11275-AS	1117	1569	AM11274-SS-NL	1255	1668
AD08095	AM11277-AS	1118	1570	AM11276-SS-NL	1256	1669
AD08096	AM11279-AS	1119	1571	AM11278-SS-NL	1257	1670
AD08097	AM11281-AS	1120	1572	AM11280-SS-NL	1258	1671
AD08098	AM11283-AS	1121	1573	AM11282-SS-NL	1259	1672
AD08099	AM11285-AS	1122	1574	AM11284-SS-NL	1260	1673
AD08100	AM11287-AS	1123	1575	AM11286-SS-NL	1261	1674
AD08101	AM11289-AS	1124	1576	AM11288-SS-NL	1262	1675
AD08102	AM11291-AS	1125	1577	AM11290-SS-NL	1263	1676
AD08103	AM11293-AS	1126	1578	AM11292-SS-NL	1264	1677
AD08173	AM10595-AS	1065	1525	AM11400-SS-NL	1265	1617
AD08174	AM11401-AS	1127	1525	AM11400-SS-NL	1265	1617
AD08175	AM11403-AS	1128	1579	AM11402-SS-NL	1266	1678
AD08176	AM11404-AS	1129	1579	AM11402-SS-NL	1266	1678
AD08177	AM11405-AS	1130	1579	AM11402-SS-NL	1266	1678
AD08224	AM11464-AS	1132	1581	AM11463-SS-NL	1267	1679
AD08225	AM11465-AS	1133	1581	AM11463-SS-NL	1267	1679
AD08226	AM11467-AS	1134	1582	AM11466-SS-NL	1268	1680
AD08227	AM11469-AS	1135	1583	AM11468-SS-NL	1269	1681
AD08228	AM11471-AS	1136	1584	AM11470-SS-NL	1270	1682
AD08229	AM11473-AS	1137	1585	AM11472-SS-NL	1271	1683
AD08230	AM11475-AS	1138	1586	AM11474-SS-NL	1272	1684
AD08231	AM11477-AS	1139	1587	AM11476-SS-NL	1273	1685
AD08232	AM11479-AS	1140	1588	AM11478-SS-NL	1274	1686
AD08233	AM11481-AS	1141	1589	AM11480-SS-NL	1275	1687
AD08243	AM11495-AS	1142	1590	AM11400-SS-NL	1265	1617
AD08244	AM11496-AS	1143	1525	AM11400-SS-NL	1265	1617

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD08245	AM11498-AS	1144	1591	AM11497-SS-NL	1276	1688
AD08246	AM11499-AS	1145	1591	AM11497-SS-NL	1276	1688
AD08420	AM11742-AS	1148	1566	AM11265-SS-NL	1251	1664
AD08421	AM11742-AS	1148	1566	AM11263-SS-NL	1250	1663
AD08422	AM11742-AS	1148	1566	AM11743-SS-NL	1278	1664
AD08423	AM11272-AS	1116	1568	AM11744-SS-NL	1279	1667
AD08424	AM11745-AS	1149	1568	AM11744-SS-NL	1279	1667
AD08468	AM11821-AS	1150	1589	AM11480-SS-NL	1275	1687
AD08469	AM11823-AS	1151	1589	AM11822-SS-NL	1280	1687
AD08470	AM11825-AS	1152	1593	AM11824-SS-NL	1281	1690
AD08564	AM11971-AS	1153	1594	AM11970-SS-NL	1282	1691
AD08565	AM11973-AS	1154	1595	AM11972-SS-NL	1283	1692
AD08566	AM11975-AS	1155	1596	AM11974-SS-NL	1284	1693
AD08567	AM11977-AS	1156	1597	AM11976-SS-NL	1285	1694
AD08568	AM11979-AS	1157	1598	AM11978-SS-NL	1286	1695
AD08569	AM07100-AS	1716	1566	AM11980-SS-NL	1287	1664
AD08570	AM11982-AS	1158	1599	AM11981-SS-NL	1288	1696
AD08571	AM11984-AS	1159	1600	AM11983-SS-NL	1289	1697
AD08572	AM07104-AS	1717	1568	AM11985-SS-NL	1290	1667
AD08573	AM11986-AS	1160	1568	AM11985-SS-NL	1290	1667
AD08662	AM12158-AS	1161	1601	AM12157-SS-NL	1291	1698
AD08663	AM12159-AS	1162	1601	AM12157-SS-NL	1291	1698
AD08664	AM12161-AS	1163	1601	AM12160-SS-NL	1292	1698
AD08665	AM12162-AS	1164	1601	AM12160-SS-NL	1292	1698
AD08666	AM12163-AS	1165	1535	AM10767-SS-NL	1215	1632
AD08667	AM12165-AS	1166	1535	AM12164-SS-NL	1293	1632
AD08668	AM12166-AS	1167	1535	AM12164-SS-NL	1293	1632
AD08669	AM12167-AS	1168	1535	AM12164-SS-NL	1293	1632
AD08670	AM12167-AS	1168	1535	AM12168-SS-NL	1294	1699
AD08671	AM12169-AS	1169	1571	AM11278-SS-NL	1257	1670
AD08672	AM12171-AS	1170	1571	AM12170-SS-NL	1295	1670
AD08673	AM12172-AS	1171	1571	AM12170-SS-NL	1295	1670
AD08674	AM12173-AS	1172	1534	AM10765-SS-NL	1214	1631
AD08675	AM12175-AS	1173	1534	AM12174-SS-NL	1296	1631
AD08676	AM12176-AS	1174	1534	AM12174-SS-NL	1296	1631
AD08677	AM12177-AS	1175	1534	AM12174-SS-NL	1296	1631
AD08678	AM12178-AS	1176	1568	AM11270-SS-NL	1254	1667
AD08679	AM12178-AS	1176	1568	AM12179-SS-NL	1297	1700
AD08680	AM12180-AS	1177	1568	AM11270-SS-NL	1254	1667
AD08681	AM12181-AS	1178	1568	AM11270-SS-NL	1254	1667

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD08682	AM12182-AS	1179	1602	AM11270-SS-NL	1254	1667
AD08687	AM12189-AS	1180	1603	AM12188-SS-NL	1298	1701
AD08688	AM12191-AS	1181	1604	AM12190-SS-NL	1299	1702
AD08689	AM12193-AS	1182	1605	AM12192-SS-NL	1300	1703
AD08690	AM12195-AS	1183	1606	AM12194-SS-NL	1301	1704
AD08691	AM12197-AS	1184	1607	AM12196-SS-NL	1302	1705
AD08692	AM12197-AS	1184	1607	AM12198-SS-NL	1303	1706
AD08889	AM11401-AS	1127	1525	AM10594-SS-NL	1200	1617
AD08890	AM12516-AS	1185	1525	AM12515-SS-NL	1304	1617
AD08891	AM12516-AS	1185	1525	AM12517-SS-NL	1305	1617
AD08892	AM12516-AS	1185	1525	AM12518-SS-NL	1306	1617
AD08893	AM12519-AS	1186	1525	AM12518-SS-NL	1306	1617
AD08894	AM12516-AS	1185	1525	AM12520-SS-NL	1307	1707
AD08895	AM12516-AS	1185	1525	AM12521-SS-NL	1308	1708
AD08896	AM12516-AS	1185	1525	AM12522-SS-NL	1309	1709
AD08897	AM12516-AS	1185	1525	AM12523-SS-NL	1310	1617
AD08951	AM12165-AS	1166	1535	AM12605-SS-NL	1311	1632
AD08952	AM12165-AS	1166	1535	AM12606-SS-NL	1312	1632
AD08953	AM12608-AS	1187	1608	AM12607-SS-NL	1313	1710
AD08954	AM12609-AS	1188	1535	AM12164-SS-NL	1293	1632
AD08955	AM12610-AS	1189	1535	AM12164-SS-NL	1293	1632
AD08956	AM12611-AS	1190	1535	AM12164-SS-NL	1293	1632
AD08957	AM12612-AS	1191	1535	AM12164-SS-NL	1293	1632
AD09240	AM12165-AS	1166	1535	AM13074-SS-NL	1315	1632
AD09241	AM12612-AS	1191	1535	AM13074-SS-NL	1315	1632
AD09863	AM11401-AS	1127	1525	AM14080-SS-NL	1316	1617
AD09864	AM11401-AS	1127	1525	AM14081-SS-NL	1317	1711
AD09865	AM11401-AS	1127	1525	AM14084-SS-NL	1318	1712

[0148] Table 8B. MUC5AC RNAi Agent Duplexes with Corresponding Sense and Antisense Strand ID Numbers and Sequence ID numbers for the modified and unmodified nucleotide sequences.)

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07626	AM10579-AS	1057	1517	AM10578-SS	1319	1609
AD07627	AM10581-AS	1058	1518	AM10580-SS	1320	1610
AD07628	AM10583-AS	1059	1519	AM10582-SS	1321	1611

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07629	AM10585-AS	1060	1520	AM10584-SS	1322	1612
AD07630	AM10587-AS	1061	1521	AM10586-SS	1323	1613
AD07631	AM10589-AS	1062	1522	AM10588-SS	1324	1614
AD07632	AM10591-AS	1063	1523	AM10590-SS	1325	1615
AD07633	AM10593-AS	1064	1524	AM10592-SS	1326	1616
AD07634	AM10595-AS	1065	1525	AM10594-SS	1327	1617
AD07635	AM10597-AS	1066	1526	AM10596-SS	1328	1618
AD07636	AM10599-AS	1067	1527	AM10598-SS	1329	1619
AD07637	AM10601-AS	1068	1528	AM10600-SS	1330	1620
AD07638	AM10603-AS	1069	1529	AM10602-SS	1331	1621
AD07639	AM10605-AS	1070	1529	AM10604-SS	1332	1622
AD07716	AM10739-AS	1071	1530	AM10738-SS	1333	1623
AD07717	AM10741-AS	1072	1530	AM10740-SS	1334	1624
AD07718	AM10743-AS	1073	1531	AM10742-SS	1335	1625
AD07719	AM10744-AS	1074	1531	AM10742-SS	1335	1625
AD07720	AM10743-AS	1073	1531	AM10745-SS	1336	1626
AD07721	AM10747-AS	1075	1532	AM10746-SS	1337	1627
AD07722	AM10747-AS	1075	1532	AM10748-SS	1338	1628
AD07723	AM10747-AS	1075	1532	AM10749-SS	1339	1629
AD07731	AM10764-AS	1076	1533	AM10763-SS	1340	1630
AD07732	AM10766-AS	1077	1534	AM10765-SS	1341	1631
AD07733	AM10768-AS	1078	1535	AM10767-SS	1342	1632
AD07734	AM10770-AS	1079	1536	AM10769-SS	1343	1633
AD07735	AM10772-AS	1080	1537	AM10771-SS	1344	1634
AD07744	AM10790-AS	1081	1538	AM10789-SS	1345	1635
AD07745	AM10792-AS	1082	1539	AM10791-SS	1346	1636
AD07746	AM10794-AS	1083	1540	AM10793-SS	1347	1637
AD07747	AM10796-AS	1084	1541	AM10795-SS	1348	1638
AD07748	AM10798-AS	1085	1542	AM10797-SS	1349	1639
AD07749	AM10800-AS	1086	1543	AM10799-SS	1350	1640
AD07750	AM10802-AS	1087	1544	AM10801-SS	1351	1641
AD07751	AM10804-AS	1088	1545	AM10803-SS	1352	1642
AD07752	AM10806-AS	1089	1546	AM10805-SS	1353	1643
AD07753	AM10808-AS	1090	1530	AM10807-SS	1354	1623
AD07754	AM10810-AS	1091	1547	AM10809-SS	1355	1644
AD07755	AM10812-AS	1092	1548	AM10811-SS	1356	1645
AD07756	AM10814-AS	1093	1549	AM10813-SS	1357	1646
AD07757	AM10816-AS	1094	1550	AM10815-SS	1358	1647
AD07758	AM10818-AS	1095	1532	AM10817-SS	1359	1627

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07760	AM10821-AS	1096	1551	AM10820-SS	1361	1648
AD07761	AM10823-AS	1097	1552	AM10822-SS	1362	1649
AD07762	AM10825-AS	1098	1553	AM10824-SS	1363	1650
AD07763	AM10827-AS	1099	1554	AM10826-SS	1364	1651
AD07764	AM10829-AS	1100	1555	AM10828-SS	1365	1652
AD07765	AM10831-AS	1101	1556	AM10830-SS	1366	1653
AD07766	AM10833-AS	1102	1557	AM10832-SS	1367	1654
AD07767	AM10835-AS	1103	1558	AM10834-SS	1368	1655
AD07768	AM10837-AS	1104	1559	AM10836-SS	1369	1656
AD07769	AM10839-AS	1105	1560	AM10838-SS	1370	1657
AD07770	AM10841-AS	1106	1561	AM10840-SS	1371	1658
AD07771	AM10843-AS	1107	1562	AM10842-SS	1372	1659
AD07772	AM10845-AS	1108	1563	AM10844-SS	1373	1660
AD07773	AM10847-AS	1109	1564	AM10846-SS	1374	1661
AD07774	AM10849-AS	1110	1565	AM10848-SS	1375	1662
AD07941	AM11065-AS	1111	1531	AM10819-SS	1360	1625
AD08083	AM11264-AS	1112	1566	AM11263-SS	1377	1663
AD08084	AM11264-AS	1112	1566	AM11265-SS	1378	1664
AD08085	AM11266-AS	1113	1566	AM11263-SS	1377	1663
AD08086	AM11268-AS	1114	1567	AM11267-SS	1379	1665
AD08087	AM11268-AS	1114	1567	AM11269-SS	1380	1666
AD08088	AM11271-AS	1115	1568	AM11270-SS	1381	1667
AD08089	AM11272-AS	1116	1568	AM11270-SS	1381	1667
AD08094	AM11275-AS	1117	1569	AM11274-SS	1382	1668
AD08095	AM11277-AS	1118	1570	AM11276-SS	1383	1669
AD08096	AM11279-AS	1119	1571	AM11278-SS	1384	1670
AD08097	AM11281-AS	1120	1572	AM11280-SS	1385	1671
AD08098	AM11283-AS	1121	1573	AM11282-SS	1386	1672
AD08099	AM11285-AS	1122	1574	AM11284-SS	1387	1673
AD08100	AM11287-AS	1123	1575	AM11286-SS	1388	1674
AD08101	AM11289-AS	1124	1576	AM11288-SS	1389	1675
AD08102	AM11291-AS	1125	1577	AM11290-SS	1390	1676
AD08103	AM11293-AS	1126	1578	AM11292-SS	1391	1677
AD08173	AM10595-AS	1065	1525	AM11400-SS	1392	1617
AD08174	AM11401-AS	1127	1525	AM11400-SS	1392	1617
AD08175	AM11403-AS	1128	1579	AM11402-SS	1393	1678
AD08176	AM11404-AS	1129	1579	AM11402-SS	1393	1678
AD08177	AM11405-AS	1130	1579	AM11402-SS	1393	1678
AD08224	AM11464-AS	1132	1581	AM11463-SS	1394	1679
AD08225	AM11465-AS	1133	1581	AM11463-SS	1394	1679

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD08226	AM11467-AS	1134	1582	AM11466-SS	1395	1680
AD08227	AM11469-AS	1135	1583	AM11468-SS	1396	1681
AD08228	AM11471-AS	1136	1584	AM11470-SS	1397	1682
AD08229	AM11473-AS	1137	1585	AM11472-SS	1398	1683
AD08230	AM11475-AS	1138	1586	AM11474-SS	1399	1684
AD08231	AM11477-AS	1139	1587	AM11476-SS	1400	1685
AD08232	AM11479-AS	1140	1588	AM11478-SS	1401	1686
AD08233	AM11481-AS	1141	1589	AM11480-SS	1402	1687
AD08243	AM11495-AS	1142	1590	AM11400-SS	1392	1617
AD08244	AM11496-AS	1143	1525	AM11400-SS	1392	1617
AD08245	AM11498-AS	1144	1591	AM11497-SS	1403	1688
AD08246	AM11499-AS	1145	1591	AM11497-SS	1403	1688
AD08420	AM11742-AS	1148	1566	AM11265-SS	1378	1664
AD08421	AM11742-AS	1148	1566	AM11263-SS	1377	1663
AD08422	AM11742-AS	1148	1566	AM11743-SS	1405	1664
AD08423	AM11272-AS	1116	1568	AM11744-SS	1406	1667
AD08424	AM11745-AS	1149	1568	AM11744-SS	1406	1667
AD08468	AM11821-AS	1150	1589	AM11480-SS	1402	1687
AD08469	AM11823-AS	1151	1589	AM11822-SS	1407	1687
AD08470	AM11825-AS	1152	1593	AM11824-SS	1408	1690
AD08564	AM11971-AS	1153	1594	AM11970-SS	1409	1691
AD08565	AM11973-AS	1154	1595	AM11972-SS	1410	1692
AD08566	AM11975-AS	1155	1596	AM11974-SS	1411	1693
AD08567	AM11977-AS	1156	1597	AM11976-SS	1412	1694
AD08568	AM11979-AS	1157	1598	AM11978-SS	1413	1695
AD08569	AM07100-AS	1716	1566	AM11980-SS	1414	1664
AD08570	AM11982-AS	1158	1599	AM11981-SS	1415	1696
AD08571	AM11984-AS	1159	1600	AM11983-SS	1416	1697
AD08572	AM07104-AS	1717	1568	AM11985-SS	1417	1667
AD08573	AM11986-AS	1160	1568	AM11985-SS	1417	1667
AD08662	AM12158-AS	1161	1601	AM12157-SS	1418	1698
AD08663	AM12159-AS	1162	1601	AM12157-SS	1418	1698
AD08664	AM12161-AS	1163	1601	AM12160-SS	1419	1698
AD08665	AM12162-AS	1164	1601	AM12160-SS	1419	1698
AD08666	AM12163-AS	1165	1535	AM10767-SS	1342	1632
AD08667	AM12165-AS	1166	1535	AM12164-SS	1420	1632
AD08668	AM12166-AS	1167	1535	AM12164-SS	1420	1632
AD08669	AM12167-AS	1168	1535	AM12164-SS	1420	1632
AD08670	AM12167-AS	1168	1535	AM12168-SS	1421	1699
AD08671	AM12169-AS	1169	1571	AM11278-SS	1384	1670

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD08672	AM12171-AS	1170	1571	AM12170-SS	1422	1670
AD08673	AM12172-AS	1171	1571	AM12170-SS	1422	1670
AD08674	AM12173-AS	1172	1534	AM10765-SS	1341	1631
AD08675	AM12175-AS	1173	1534	AM12174-SS	1423	1631
AD08676	AM12176-AS	1174	1534	AM12174-SS	1423	1631
AD08677	AM12177-AS	1175	1534	AM12174-SS	1423	1631
AD08678	AM12178-AS	1176	1568	AM11270-SS	1381	1667
AD08679	AM12178-AS	1176	1568	AM12179-SS	1424	1700
AD08680	AM12180-AS	1177	1568	AM11270-SS	1381	1667
AD08681	AM12181-AS	1178	1568	AM11270-SS	1381	1667
AD08682	AM12182-AS	1179	1602	AM11270-SS	1381	1667
AD08687	AM12189-AS	1180	1603	AM12188-SS	1425	1701
AD08688	AM12191-AS	1181	1604	AM12190-SS	1426	1702
AD08689	AM12193-AS	1182	1605	AM12192-SS	1427	1703
AD08690	AM12195-AS	1183	1606	AM12194-SS	1428	1704
AD08691	AM12197-AS	1184	1607	AM12196-SS	1429	1705
AD08692	AM12197-AS	1184	1607	AM12198-SS	1430	1706
AD08889	AM11401-AS	1127	1525	AM10594-SS	1327	1617
AD08890	AM12516-AS	1185	1525	AM12515-SS	1431	1617
AD08891	AM12516-AS	1185	1525	AM12517-SS	1432	1617
AD08892	AM12516-AS	1185	1525	AM12518-SS	1433	1617
AD08893	AM12519-AS	1186	1525	AM12518-SS	1433	1617
AD08894	AM12516-AS	1185	1525	AM12520-SS	1434	1707
AD08895	AM12516-AS	1185	1525	AM12521-SS	1435	1708
AD08896	AM12516-AS	1185	1525	AM12522-SS	1436	1709
AD08897	AM12516-AS	1185	1525	AM12523-SS	1437	1617
AD08951	AM12165-AS	1166	1535	AM12605-SS	1438	1632
AD08952	AM12165-AS	1166	1535	AM12606-SS	1439	1632
AD08953	AM12608-AS	1187	1608	AM12607-SS	1440	1710
AD08954	AM12609-AS	1188	1535	AM12164-SS	1420	1632
AD08955	AM12610-AS	1189	1535	AM12164-SS	1420	1632
AD08956	AM12611-AS	1190	1535	AM12164-SS	1420	1632
AD08957	AM12612-AS	1191	1535	AM12164-SS	1420	1632
AD09240	AM12165-AS	1166	1535	AM13074-SS	1441	1632
AD09241	AM12612-AS	1191	1535	AM13074-SS	1441	1632
AD09863	AM11401-AS	1127	1525	AM14080-SS	1442	1617
AD09864	AM11401-AS	1127	1525	AM14081-SS	1443	1711
AD09865	AM11401-AS	1127	1525	AM14084-SS	1444	1712

[0149] Table 8C. MUC5AC RNAi Agent Duplexes with Corresponding Sense and Antisense Strand ID Numbers and Sequence ID numbers for certain modified and unmodified nucleotide sequences tested *in vitro*.

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD07634	AM10595-AS	1065	1525	AM10594-SS-s	1445	1617
AD07637	AM10601-AS	1068	1528	AM10600-SS-s	1446	1620
AD07732	AM10766-AS	1077	1534	AM10765-SS-s	1447	1631
AD07733	AM10768-AS	1078	1535	AM10767-SS-s	1448	1632
AD07734	AM10770-AS	1079	1536	AM10769-SS-s	1449	1633
AD07735	AM10772-AS	1080	1537	AM10771-SS-s	1450	1634
AD07745	AM10792-AS	1082	1539	AM10791-SS-s	1451	1636
AD07746	AM10794-AS	1083	1540	AM10793-SS-s	1452	1637
AD07747	AM10796-AS	1084	1541	AM10795-SS-s	1453	1638
AD07748	AM10798-AS	1085	1542	AM10797-SS-s	1454	1639
AD07749	AM10800-AS	1086	1543	AM10799-SS-s	1455	1640
AD07750	AM10802-AS	1087	1544	AM10801-SS-s	1456	1641
AD07751	AM10804-AS	1088	1545	AM10803-SS-s	1457	1642
AD07756	AM10814-AS	1093	1549	AM10813-SS-s	1458	1646
AD07760	AM10821-AS	1096	1551	AM10820-SS-s	1459	1648
AD07763	AM10827-AS	1099	1554	AM10826-SS-s	1460	1651
AD07764	AM10829-AS	1100	1555	AM10828-SS-s	1461	1652
AD07766	AM10833-AS	1102	1557	AM10832-SS-s	1462	1654
AD07768	AM10837-AS	1104	1559	AM10836-SS-s	1463	1656
AD07770	AM10841-AS	1106	1561	AM10840-SS-s	1464	1658
AD07771	AM10843-AS	1107	1562	AM10842-SS-s	1465	1659
AD07772	AM10845-AS	1108	1563	AM10844-SS-s	1466	1660
AD07773	AM10847-AS	1109	1564	AM10846-SS-s	1467	1661
AD07774	AM10849-AS	1110	1565	AM10848-SS-s	1468	1662
AD08094	AM11275-AS	1117	1569	AM11274-SS-s	1469	1668
AD08095	AM11277-AS	1118	1570	AM11276-SS-s	1470	1669
AD08096	AM11279-AS	1119	1571	AM11278-SS-s	1471	1670
AD08097	AM11281-AS	1120	1572	AM11280-SS-s	1472	1671
AD08100	AM11287-AS	1123	1575	AM11286-SS-s	1473	1674
AD08101	AM11289-AS	1124	1576	AM11288-SS-s	1474	1675
AD08103	AM11293-AS	1126	1578	AM11292-SS-s	1475	1677
AD08568	AM11979-AS	1157	1598	AM11978-SS-s	1476	1695
AD08569	AM07100-AS	1716	1566	AM11980-SS-s	1477	1664
AD08571	AM11984-AS	1159	1600	AM11983-SS-s	1478	1697
AD08572	AM07104-AS	1717	1568	AM11985-SS-s	1479	1667
AD08573	AM11986-AS	1160	1568	AM11985-SS-s	1479	1667

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AD08666	AM12163-AS	1165	1535	AM10767-SS-s	1448	1632
AD08667	AM12165-AS	1166	1535	AM12164-SS-s	1480	1632
AD08668	AM12166-AS	1167	1535	AM12164-SS-s	1480	1632
AD08669	AM12167-AS	1168	1535	AM12164-SS-s	1480	1632
AD08670	AM12167-AS	1168	1535	AM12168-SS-s	1481	1699
AD08671	AM12169-AS	1169	1571	AM11278-SS-s	1471	1670
AD08672	AM12171-AS	1170	1571	AM12170-SS-s	1482	1670
AD08673	AM12172-AS	1171	1571	AM12170-SS-s	1482	1670

[0150] Table 9. MUC5AC RNAi Agent Conjugated Duplexes with Corresponding Sense and Antisense Strand ID Numbers and Sequence ID numbers for the modified and unmodified nucleotide sequences. (Shown with Targeting Ligand Conjugates)

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AC000313	AM10743-AS	1073	1531	CS000387	1483	1626
AC000431	AM11264-AS	1112	1566	CS000521	1486	1663
AC000432	AM11264-AS	1112	1566	CS000523	1487	1664
AC000433	AM11266-AS	1113	1566	CS000521	1486	1663
AC000434	AM11268-AS	1114	1567	CS000525	1488	1665
AC000435	AM11268-AS	1114	1567	CS000527	1489	1666
AC000436	AM11271-AS	1115	1568	CS000528	1490	1667
AC000437	AM11272-AS	1116	1568	CS000528	1490	1667
AC000480	AM11401-AS	1127	1525	CS000578	1491	1617
AC000482	AM10595-AS	1065	1525	CS000578	1491	1617
AC000483	AM11495-AS	1142	1590	CS000578	1491	1617
AC000484	AM11496-AS	1143	1525	CS000578	1491	1617
AC000485	AM11403-AS	1128	1579	CS000583	1492	1678
AC000486	AM11404-AS	1129	1579	CS000583	1492	1678
AC000487	AM11405-AS	1130	1579	CS000583	1492	1678
AC000502	AM11462-AS	1131	1580	CS000517	1484	1718
AC000504	AM11464-AS	1132	1581	CS000608	1493	1679
AC000505	AM11465-AS	1133	1581	CS000608	1493	1679
AC000506	AM11467-AS	1134	1582	CS000612	1494	1680
AC000507	AM11469-AS	1135	1583	CS000614	1495	1681
AC000508	AM11471-AS	1136	1584	CS000616	1496	1682
AC000509	AM11473-AS	1137	1585	CS000618	1497	1683

Duplex	AS ID	AS modified SEQ ID NO:	AS unmodified SEQ ID NO:	SS ID	SS modified SEQ ID NO:	SS unmodified SEQ ID NO:
AC000510	AM11475-AS	1138	1586	CS000620	1498	1684
AC000511	AM11477-AS	1139	1587	CS000622	1499	1685
AC000512	AM11479-AS	1140	1588	CS000624	1500	1686
AC000513	AM11481-AS	1141	1589	CS000626	1501	1687
AC000805	AM10739-AS	1071	1530	CS001001	1503	1623
AC000806	AM10741-AS	1072	1530	CS001003	1504	1624
AC000807	AM10743-AS	1073	1531	CS001005	1505	1625
AC000808	AM10744-AS	1074	1531	CS001005	1505	1625
AC000809	AM10747-AS	1075	1532	CS001007	1506	1627
AC000810	AM10747-AS	1075	1532	CS001009	1507	1628
AC000811	AM10747-AS	1075	1532	CS001010	1508	1629
AC001128	AM12178-AS	1176	1568	CS000528	1490	1667
AC001129	AM12178-AS	1176	1568	CS001401	1512	1700
AC001130	AM12180-AS	1177	1568	CS000528	1490	1667
AC001131	AM12181-AS	1178	1568	CS000528	1490	1667
AC000832	AM11742-AS	1148	1566	CS000523	1487	1664
AC000833	AM11742-AS	1148	1566	CS000521	1486	1663
AC000834	AM11742-AS	1148	1566	CS001040	1510	1664
AC000835	AM11272-AS	1116	1568	CS001041	1511	1667
AC000836	AM11745-AS	1149	1568	CS001041	1511	1667
AC001305	AM12165-AS	1166	1535	CS001644	1513	1632
AC001306	AM12612-AS	1191	1535	CS001644	1513	1632
AC001708	AM11401-AS	1127	1525	CS002194	1514	1617
AC001709	AM11401-AS	1127	1525	CS002195	1515	1711
AC001710	AM11401-AS	1127	1525	CS002196	1516	1712

[0151] Table 10A. Conjugate Duplex ID Numbers Referencing Position Targeted On MUC5AC (MUC5AC) Gene

Duplex	AS ID	SS ID	Targeted MUC5AC Gene Position (Of SEQ ID NO:1)
AC000313	AM10743-AS	CS000387	1921
AC000431	AM11264-AS	CS000521	5029
AC000432	AM11264-AS	CS000523	5029
AC000433	AM11266-AS	CS000521	5029
AC000434	AM11268-AS	CS000525	9729
AC000435	AM11268-AS	CS000527	9729
AC000436	AM11271-AS	CS000528	15052

Duplex	AS ID	SS ID	Targeted MUC5AC Gene Position (Of SEQ ID NO:1)
AC000437	AM11272-AS	CS000528	15052
AC000480	AM11401-AS	CS000578	3535
AC000482	AM10595-AS	CS000578	3535
AC000483	AM11495-AS	CS000578	3535
AC000484	AM11496-AS	CS000578	3535
AC000485	AM11403-AS	CS000583	3535
AC000486	AM11404-AS	CS000583	3535
AC000487	AM11405-AS	CS000583	3535
AC000502	AM11462-AS	CS000517	N/A (murine-specific)
AC000504	AM11464-AS	CS000608	N/A (murine-specific)
AC000505	AM11465-AS	CS000608	N/A (murine-specific)
AC000506	AM11467-AS	CS000612	N/A (murine-specific)
AC000507	AM11469-AS	CS000614	N/A (murine-specific)
AC000508	AM11471-AS	CS000616	N/A (murine-specific)
AC000509	AM11473-AS	CS000618	N/A (murine-specific)
AC000510	AM11475-AS	CS000620	N/A (murine-specific)
AC000511	AM11477-AS	CS000622	N/A (murine-specific)
AC000512	AM11479-AS	CS000624	N/A (murine-specific)
AC000513	AM11481-AS	CS000626	N/A (murine-specific)
AC000805	AM10739-AS	CS001001	304
AC000806	AM10741-AS	CS001003	304
AC000807	AM10743-AS	CS001005	1921
AC000808	AM10744-AS	CS001005	1921
AC000809	AM10747-AS	CS001007	1832
AC000810	AM10747-AS	CS001009	1832
AC000811	AM10747-AS	CS001010	1832
AC001128	AM12178-AS	CS000528	15052
AC001129	AM12178-AS	CS001401	15052
AC001130	AM12180-AS	CS000528	15052
AC001131	AM12181-AS	CS000528	15052
AC000832	AM11742-AS	CS000523	5029
AC000833	AM11742-AS	CS000521	5029
AC000834	AM11742-AS	CS001040	5029
AC000835	AM11272-AS	CS001041	15052
AC000836	AM11745-AS	CS001041	15052
AC001305	AM12165-AS	CS001644	4993
AC001306	AM12612-AS	CS001644	4993
AC001708	AM11401-AS	CS002194	3535
AC001709	AM11401-AS	CS002195	3535

Duplex	AS ID	SS ID	Targeted MUC5AC Gene Position (Of SEQ ID NO:1)
AC001710	AM11401-AS	CS002196	3535

[0152] Table 10B. Conjugate ID Numbers and Corresponding AD Duplex Numbers, Referencing Position Targeted On MUC5AC (MUC5AC) Gene

AC Duplex Number	Corresponding AD Duplex Number	Targeted MUC5AC Gene Position (Of SEQ ID NO:1)
AC000313	AD07720	1921
AC000431	AD08083	5029
AC000432	AD08084	5029
AC000433	AD08085	5029
AC000434	AD08086	9729
AC000435	AD08087	9729
AC000436	AD08088	15052
AC000437	AD08089	15052
AC000480	AD08174	3535
AC000482	AD08173	3535
AC000483	AD08243	3535
AC000484	AD08244	3535
AC000485	AD08175	3535
AC000486	AD08176	3535
AC000487	AD08177	3535
AC000502	AD08222	N/A (murine-specific)
AC000503	AD08223	N/A (murine-specific)
AC000504	AD08224	N/A (murine-specific)
AC000505	AD08225	N/A (murine-specific)
AC000506	AD08226	N/A (murine-specific)
AC000507	AD08227	N/A (murine-specific)
AC000508	AD08228	N/A (murine-specific)
AC000509	AD08229	N/A (murine-specific)
AC000510	AD08230	N/A (murine-specific)
AC000511	AD08231	N/A (murine-specific)
AC000512	AD08232	N/A (murine-specific)
AC000513	AD08233	N/A (murine-specific)
AC000805	AD07716	304
AC000806	AD07717	304
AC000807	AD07718	1921
AC000808	AD07719	1921

AC Duplex Number	Corresponding AD Duplex Number	Targeted MUC5AC Gene Position (Of SEQ ID NO:1)
AC000809	AD07721	1832
AC000810	AD07722	1832
AC000811	AD07723	1832
AC001128	AD08678	15052
AC001129	AD08679	15052
AC001130	AD08680	15052
AC001131	AD08681	15052
AC000832	AD08420	5029
AC000833	AD08421	5029
AC000834	AD08422	5029
AC000835	AD08423	15052
AC000836	AD08424	15052
AC001305	AD09240	4993
AC001306	AD09241	4993
AC001708	AD09863	3535
AC001709	AD09864	3535
AC001710	AD09865	3535

[0153] Table 11. Conjugate ID Numbers With Chemically Modified Antisense and Sense Strands (including Linkers and Conjugates)

AC ID Number	Sense Strand (Fully Modified with Conjugated Targeting Ligand) (5' → 3')	SEQ ID NO.	Antisense Strand (5' → 3')	SEQ ID NO.
AC000313	Tri-SM6.1-avb6-(TA14)gsa_2NaguaugCfUfCfaguacugias(invAb)	1483	cPrpusAfscsCfaGfuGfcUfgAfGcfaUfaCfuUfsc	1073
AC000431	Tri-SM6.1-avb6-(TA14)csugcuacaAfCfUfaugagauccas(invAb)	1486	cPrpusGfsgsAfuCfuCfaUfaGfuUfgUfaGfcAfsg	1112
AC000432	Tri-SM6.1-avb6-(TA14)csugcuacaAfCfUfaugaiauccas(invAb)	1487	cPrpusGfsgsAfuCfuCfaUfaGfuUfgUfaGfcAfsg	1112
AC000433	Tri-SM6.1-avb6-(TA14)csugcuacaAfCfUfaugagauccas(invAb)	1486	cPrpusGfsgsAfuCfuU _{um} CfaUfaGfuUfgUfaGfcAfsg	1113
AC000434	Tri-SM6.1-avb6-(TA14)csuggaccAfAfCfugguuugacas(invAb)	1488	cPrpusGfsusCfaAfaCfcAfcUfuGfgUfcCfaGfsg	1114
AC000435	Tri-SM6.1-avb6-(TA14)csuggaccAfAfCfugguuuiacas(invAb)	1489	cPrpusGfsusCfaAfaCfcAfcUfuGfgUfcCfaGfsg	1114
AC000436	Tri-SM6.1-avb6-(TA14)csugaucaUfCfUfucaacaacaas(invAb)	1490	cPrpusUfsgsUfuGfuUfgAfaGfaUfgAfuCfuCfsg	1115
AC000437	Tri-SM6.1-avb6-(TA14)csugaucaUfCfUfucaacaacaas(invAb)	1490	cPrpusUfsgsUfuguugaaGfaUfgAfucucsg	1116
AC000480	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1491	cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1127
AC000482	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1491	usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1065
AC000483	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1491	cPrpusUfsgsUfaGfuAfgUfcicAfgAfaCfaGfsc	1142
AC000484	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1491	cPrpusUfsgsUfaGfuAfgUfcgAfgAfaCfaGfsc	1143
AC000485	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1492	usUfsgsUfaGfuAfgUfcAfcAfgAfaCfaGfsc	1128
AC000486	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1492	cPrpusUfsgsUfaGfuAfgUfcAfcAfgAfaCfaGfsc	1129
AC000487	Tri-SM6.1-avb6-(TA14)gscuguucUfCfGfacuacuacaas(invAb)	1492	cPrpusUfsgsuaguagucAfcAfcAfcagsg	1130
AC000502	Tri-SM6.1-avb6-(TA14)asccauuguGfCfUfacaacuauugas(invAb)	1484	cPrpusCfsasuaguuguaGfcAfcAfcugggsu	1131
AC000503	Tri-SM6.1-avb6-(TA14)asccagaucaUfCfuucaacaacas(invAb)	1493	usGfsusUfgUfuGfaAfgAfuGfaUfcUfgGfsu	1715
AC000504	Tri-SM6.1-avb6-(TA14)asccagaucaUfCfuucaacaacas(invAb)	1493	cPrpusGfsusUfgUfuGfaAfgAfuGfaUfcUfgGfsu	1132

AC000505	Tri-SM6.1-avb6-(TA14)ascagauAFUfcuuaacaacas(invAb)	1493	cPrpusGfsusuguugaagAFuGfaUfcuggsu	1133
AC000506	Tri-SM6.1-avb6-(TA14)gsgcucuguGfGfUfaacuuaacas(invAb)	1494	cPrpusGfsusUfgAFaGfuUfaCfcAfcAfgAfsc	1134
AC000507	Tri-SM6.1-avb6-(TA14)gsagcuggAFGfAfaugaagaaas(invAb)	1495	cPrpusAfcscUfuUfuCfaUfuCfuCfcAfcGfcUfsc	1135
AC000508	Tri-SM6.1-avb6-(TA14)gsggagauGfAFaagaugcuas(invAb)	1496	cPrpusAfcscCfaUfaCfuUfuUfcAfuUfcUfcCfsc	1136
AC000509	Tri-SM6.1-avb6-(TA14)csuucucgaAFcfUfgcaugauagas(invAb)	1497	cPrpusCfsasUfaCfaUfgCfaGfuUfcGfaGfaAfs	1137
AC000510	Tri-SM6.1-avb6-(TA14)gscucgaacUfGfCfaugauagacas(invAb)	1498	cPrpusGfsusCfaUfaCfaUfgCfaGfuUfcGfaGfsc	1138
AC000511	Tri-SM6.1-avb6-(TA14)csucgaacuGfCfAfaugauagacaas(invAb)	1499	cPrpusUfsgsUfcAfuAfcAfuGfcAfgUfuCfGfAfs	1139
AC000512	Tri-SM6.1-avb6-(TA14)cscacuguuCfUfgfugacuacuaas(invAb)	1500	cPrpusUfscsGfuAfgUfcAfcAfcAfgAfaCfaGfuGfsc	1140
AC000513	Tri-SM6.1-avb6-(TA14)csacuguuCfUfgfugacuacuaas(invAb)	1501	cPrpusGfsusAfgUfaGfuCfaCfaGfaAfcAfgUfsc	1141
AC000805	Tri-SM6.1-avb6-(TA14)csagcuuccAFcfUfacaiaacuu(invAb)	1503	cPrpasAfcscGfuCfuUfgUfaGfuGfgAfaGfcUfsc	1071
AC000806	Tri-SM6.1-avb6-(TA14)csagcuuccAFcfUfacaagacuu(invAb)	1504	cPrpasAfcscGfuCfuU _{UNA} UfgUfaGfuGfgAfaGfcUfsc	1072
AC000807	Tri-SM6.1-avb6-(TA14)gsa_2NaguaugCfUfCfagcacugias(invAb)	1505	cPrpusAfcscCfaGfuGfcUfgAfgCfaUfaCfuUfsc	1073
AC000808	Tri-SM6.1-avb6-(TA14)gsa_2NaguaugCfUfCfagcacugias(invAb)	1505	cPrpusAfcscCfaGfuGfcU _{UNA} GfcUfgAfgCfaUfaCfuUfsc	1074
AC000809	Tri-SM6.1-avb6-(TA14)gsccuuccAFafAfcacuucaaaas(invAb)	1506	cPrpusUfscsGfaAfgguguUfgAfaGfaAfgGfsc	1075
AC000810	Tri-SM6.1-avb6-(TA14)gsccuuccAFafAfcacuucaaaas(invAb)	1507	cPrpusUfscsGfaAfgguguUfgAfaGfaAfgGfsc	1075
AC000811	Tri-SM6.1-avb6-(TA14)gsccuuccAFafAfcacuucaaaas(invAb)	1508	cPrpusUfscsGfaAfgguguUfgAfaGfaAfgGfsc	1075
AC000832	Tri-SM6.1-avb6-(TA14)csugcuacaAFcfUfaugaiauccas(invAb)	1487	cPrpusGfsgsaucucuaGfuUfgUfagcasg	1148
AC000833	Tri-SM6.1-avb6-(TA14)csugcuacaAFcfUfaugaiauccas(invAb)	1486	cPrpusGfsgsaucucuaGfuUfgUfagcasg	1148
AC000834	Tri-SM6.1-avb6-(TA14)csugcuacaAFcfUfaugaiauccas(invAb)	1510	cPrpusGfsgsaucucuaGfuUfgUfagcasg	1148
AC000835	Tri-SM6.1-avb6-(TA14)csgagauCfaUfcUfucaacaacaas(invAb)	1511	cPrpusUfsgsUfuguugaGfaUfgAfucucsg	1116
AC000836	Tri-SM6.1-avb6-(TA14)csgagauCfaUfcUfucaacaacaas(invAb)	1511	cPrpusUfsgsuuguugaGfaUfgAfucucsg	1149

AC001128	Tri-SM6.1-avb6-(TA14)csgagaucaUfCfUfucaacaacaas(invAb)	1490	cPrpusUfsgsUfugU _{UN} ugaaGfaUfgAfucucsg	1176
AC001129	Tri-SM6.1-avb6-(TA14)csgagaucaUfCfUfuca_2Nacaacaas(invAb)	1512	cPrpusUfsgsUfugU _{UN} ugaaGfaUfgAfucucsg	1176
AC001130	Tri-SM6.1-avb6-(TA14)csgagaucaUfCfUfucaacaacaas(invAb)	1490	cPrpusUfsgsUfugU _{UN} ugaaGfaUfgAfucucsg	1177
AC001131	Tri-SM6.1-avb6-(TA14)csgagaucaUfCfUfucaacaacaas(invAb)	1490	cPrpusUfsgsUfU _{UN} guugaaGfaUfgAfucucsg	1178
AC001305	Tri-SM6.1-avb6-(TA14)gscugauUfuGfcCfugaacaagaas(invAb)	1513	usUfscsuuguucagGfcAfaAfucagsc	1166
AC001306	Tri-SM6.1-avb6-(TA14)gscugauUfuGfcCfugaacaagaas(invAb)	1513	cPrpuUfcuuuguucagGfcAfaAfucagsc	1191
AC001708	Tri-SM6.1-avb6-(TA14)gscuguucuGfcGfacuacuacaa(invAb)	1514	cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1127
AC001709	Tri-SM6.1-avb6-(TA14)gscugguucuGfcGfacuacuacaa(invAb)	1515	cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1127
AC001710	Tri-SM6.1-avb6-(TA14)gscguucuGfcGfacuacuacaa(invAb)	1516	cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc	1127

[0154] In some embodiments, a MUC5AC RNAi agent is prepared or provided as a salt, mixed salt, or a free-acid. In some embodiments, a MUC5AC RNAi agent is prepared or provided as a pharmaceutically acceptable salt. In some embodiments, a MUC5AC RNAi agent is prepared or provided as a pharmaceutically acceptable sodium or potassium salt. The RNAi agents described herein, upon delivery to a cell expressing an MUC5AC gene, inhibit or knockdown expression of one or more MUC5AC genes *in vivo* and/or *in vitro*.

Targeting Groups, Linking Groups, Pharmacokinetic/Pharmacodynamic (PK/PD) Modulators, and Delivery Vehicles

[0155] In some embodiments, a MUC5AC RNAi agent contains or is conjugated to one or more non-nucleotide groups including, but not limited to, a targeting group, a linking group, a pharmacokinetic/pharmacodynamic (PK/PD) modulator, a delivery polymer, or a delivery vehicle. The non-nucleotide group can enhance targeting, delivery, or attachment of the RNAi agent. The non-nucleotide group can be covalently linked to the 3' and/or 5' end of either the sense strand and/or the antisense strand. In some embodiments, a MUC5AC RNAi agent contains a non-nucleotide group linked to the 3' and/or 5' end of the sense strand. In some embodiments, a non-nucleotide group is linked to the 5' end of a MUC5AC RNAi agent sense strand. A non-nucleotide group can be linked directly or indirectly to the RNAi agent via a linker/linking group. In some embodiments, a non-nucleotide group is linked to the RNAi agent via a labile, cleavable, or reversible bond or linker.

[0156] In some embodiments, a non-nucleotide group enhances the pharmacokinetic or biodistribution properties of an RNAi agent or conjugate to which it is attached to improve cell- or tissue-specific distribution and cell-specific uptake of the conjugate. In some embodiments, a non-nucleotide group enhances endocytosis of the RNAi agent.

[0157] Targeting groups or targeting moieties enhance the pharmacokinetic or biodistribution properties of a conjugate or RNAi agent to which they are attached to improve cell-specific (including, in some cases, organ specific) distribution and cell-specific (or organ specific) uptake of the conjugate or RNAi agent. A targeting group can be monovalent, divalent, trivalent, tetravalent, or have higher valency for the target to which it is directed. Representative targeting groups include, without limitation, compounds with affinity to cell surface molecule, cell receptor ligands, hapten, antibodies, monoclonal antibodies, antibody fragments, and antibody mimics with affinity to cell surface molecules. In some embodiments, a targeting group is linked to an RNAi agent using a linker, such as

a PEG linker or one, two, or three abasic and/or ribitol (abasic ribose) residues, which in some instances can serve as linkers.

[0158] A targeting group, with or without a linker, can be attached to the 5' or 3' end of any of the sense and/or antisense strands disclosed in Tables 2, 3, 4, 5, 6, 7, and 11. A linker, with or without a targeting group, can be attached to the 5' or 3' end of any of the sense and/or antisense strands disclosed in Tables 2, 3, 4, 5, 6, 7, and 11.

[0159] The MUC5AC RNAi agents described herein can be synthesized having a reactive group, such as an amino group (also referred to herein as an amine), at the 5'-terminus and/or the 3'-terminus. The reactive group can be used subsequently to attach a targeting moiety using methods typical in the art.

[0160] For example, in some embodiments, the MUC5AC RNAi agents disclosed herein can be synthesized having an $\text{NH}_2\text{-C}_6$ group at the 5'-terminus of the sense strand of the RNAi agent. The terminal amino group subsequently can be reacted to form a conjugate with, for example, a group that includes an $\alpha\text{v}\beta 6$ integrin targeting ligand. In some embodiments, the MUC5AC RNAi agents disclosed herein are synthesized having one or more alkyne groups at the 5'-terminus of the sense strand of the RNAi agent. The terminal alkyne group(s) can subsequently be reacted to form a conjugate with, for example, a group that includes an $\alpha\text{v}\beta 6$ integrin targeting ligand.

[0161] In some embodiments, a targeting group comprises an integrin targeting ligand. In some embodiments, an integrin targeting ligand is an $\alpha\text{v}\beta 6$ integrin targeting ligand. The use of an $\alpha\text{v}\beta 6$ integrin targeting ligand facilitates cell-specific targeting to cells having $\alpha\text{v}\beta 6$ on its respective surface, and binding of the integrin targeting ligand can facilitate entry of the therapeutic agent, such as an RNAi agent, to which it is linked, into cells such as epithelial cells, including pulmonary epithelial cells and renal epithelial cells. Integrin targeting ligands can be monomeric or monovalent (e.g., having a single integrin targeting moiety) or multimeric or multivalent (e.g., having multiple integrin targeting moieties). The targeting group can be attached to the 3' and/or 5' end of the RNAi oligonucleotide using methods known in the art. The preparation of targeting groups, such as $\alpha\text{v}\beta 6$ integrin targeting ligands, is described, for example, in International Patent Application Publication No. WO 2018/085415 and in International Patent Application Publication No. WO 2019/089765, the contents of each of which are incorporated herein in its entirety.

[0162] In some embodiments, targeting groups are linked to the MUC5AC RNAi agents without the use of an additional linker. In some embodiments, the targeting group is

designed having a linker readily present to facilitate the linkage to a MUC5AC RNAi agent. In some embodiments, when two or more RNAi agents are included in a composition, the two or more RNAi agents can be linked to their respective targeting groups using the same linkers. In some embodiments, when two or more RNAi agents are included in a composition, the two or more RNAi agents are linked to their respective targeting groups using different linkers.

[0163] In some embodiments, a linking group is conjugated to the RNAi agent. The linking group facilitates covalent linkage of the agent to a targeting group, pharmacokinetic modulator, delivery polymer, or delivery vehicle. The linking group can be linked to the 3' and/or the 5' end of the RNAi agent sense strand or antisense strand. In some embodiments, the linking group is linked to the RNAi agent sense strand. In some embodiments, the linking group is conjugated to the 5' or 3' end of an RNAi agent sense strand. In some embodiments, a linking group is conjugated to the 5' end of an RNAi agent sense strand. Examples of linking groups, include but are not limited to: C6-SS-C6, 6-SS-6, reactive groups such as primary amines (e.g., NH₂-C6) and alkynes, alkyl groups, abasic residues/nucleotides, amino acids, tri-alkyne functionalized groups, ribitol, and/or PEG groups. Examples of certain linking groups are provided in Table 12.

[0164] A linker or linking group is a connection between two atoms that links one chemical group (such as an RNAi agent) or segment of interest to another chemical group (such as a targeting group, pharmacokinetic modulator, or delivery polymer) or segment of interest via one or more covalent bonds. A labile linkage contains a labile bond. A linkage can optionally include a spacer that increases the distance between the two joined atoms. A spacer may further add flexibility and/or length to the linkage. Spacers include, but are not limited to, alkyl groups, alkenyl groups, alkynyl groups, aryl groups, aralkyl groups, aralkenyl groups, and aralkynyl groups; each of which can contain one or more heteroatoms, heterocycles, amino acids, nucleotides, and saccharides. Spacer groups are well known in the art and the preceding list is not meant to limit the scope of the description. In some embodiments, a MUC5AC RNAi agent is conjugated to a polyethylene glycol (PEG) moiety, or to a hydrophobic group having 12 or more carbon atoms, such as a cholesterol or palmitoyl group.

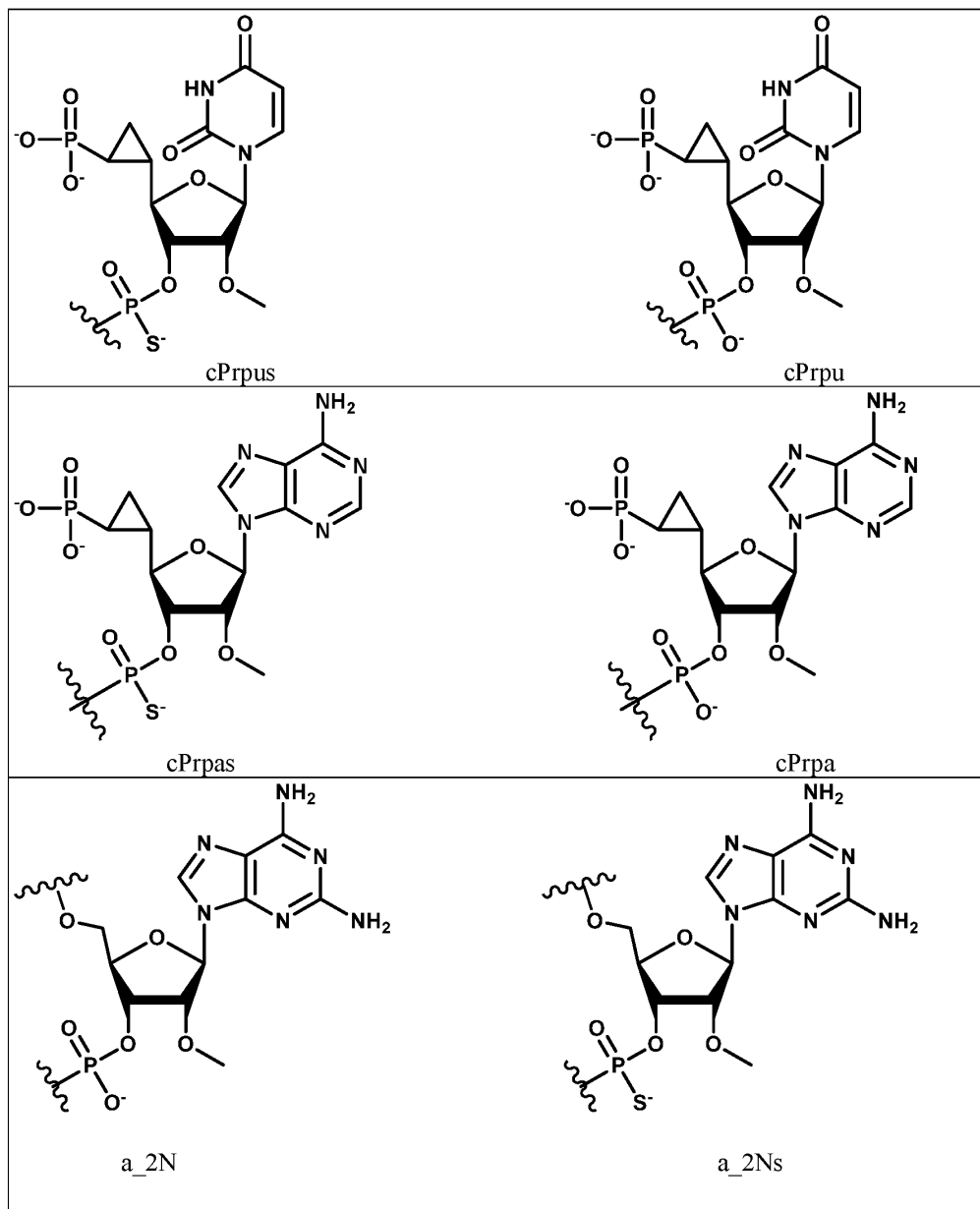
[0165] In some embodiments, a MUC5AC RNAi agent is linked to one or more pharmacokinetic/pharmacodynamic (PK/PD) modulators. PK/PD modulators can increase circulation time of the conjugated drug and/or increase the activity of the RNAi agent

through improved cell receptor binding, improved cellular uptake, and/or other means. Various PK/PD modulators suitable for use with RNAi agents are known in the art. In some embodiments, the PK/PD modulatory can be cholesterol or cholesteryl derivatives, or in some circumstances a PK/PD modulator can be comprised of alkyl groups, alkenyl groups, alkynyl groups, aryl groups, aralkyl groups, aralkenyl groups, or aralkynyl groups, each of which may be linear, branched, cyclic, and/or substituted or unsubstituted. In some embodiments, the location of attachment for these moieties is at the 5' or 3' end of the sense strand, at the 2' position of the ribose ring of any given nucleotide of the sense strand, and/or attached to the phosphate or phosphorothioate backbone at any position of the sense strand.

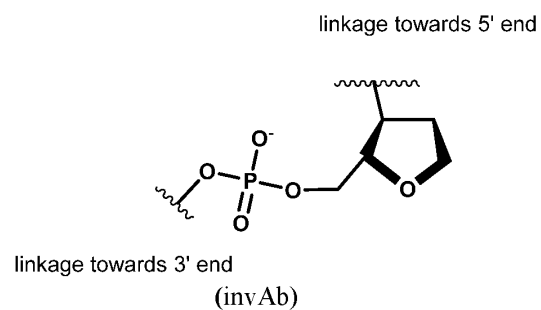
[0166] Any of the MUC5AC RNAi agent nucleotide sequences listed in Tables 2, 3, 4, 5, 6, 7, and 11, whether modified or unmodified, can contain 3' and/or 5' targeting group(s), linking group(s), and/or PK/PD modulator(s). Any of the MUC5AC RNAi agent sequences listed in Tables 3, 4, 5, 6, 7, and 11, or are otherwise described herein, which contain a 3' or 5' targeting group, linking group, and/or PK/PD modulator can alternatively contain no 3' or 5' targeting group, linking group, or PK/PD modulator, or can contain a different 3' or 5' targeting group, linking group, or pharmacokinetic modulator including, but not limited to, those depicted in Table 12. Any of the MUC5AC RNAi agent duplexes listed in Tables 8A, 8B, 8C, 9, 10A, 10B, and 11, whether modified or unmodified, can further comprise a targeting group or linking group, including, but not limited to, those depicted in Table 11, and the targeting group or linking group can be attached to the 3' or 5' terminus of either the sense strand or the antisense strand of the MUC5AC RNAi agent duplex.

[0167] Examples of certain modified nucleotides, capping moieties, and linking groups are provided in Table 12.

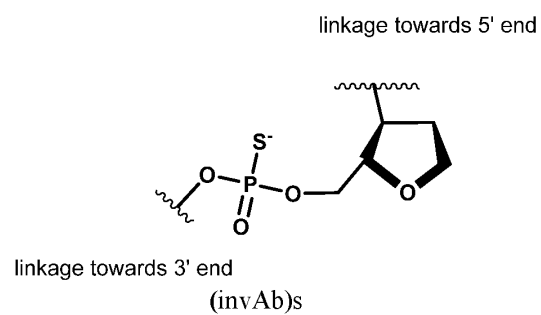
Table 12. Structures Representing Various Modified Nucleotides, Capping Moieties, and Linking Groups (wherein ζ indicates the point of connection)



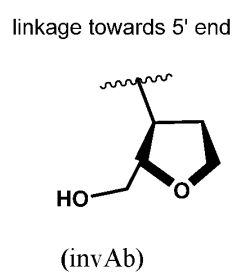
When positioned internally:



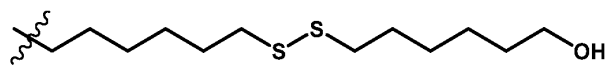
When positioned internally:



When positioned at the 3' terminal end:



When positioned at the 3' terminal end:



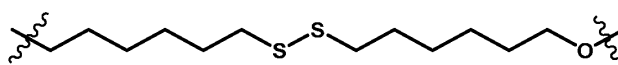
linkage towards 5' end

(C6-SS-C6)

When positioned internally:

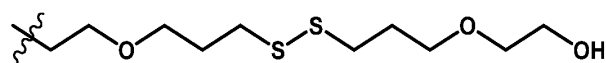
linkage towards 5' end

linkage towards 3' end



(C6-SS-C6)

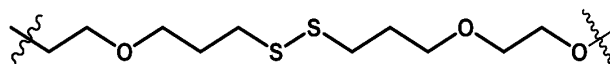
When positioned at the 3' terminal end:



linkage towards 5' end

(6-SS-6)

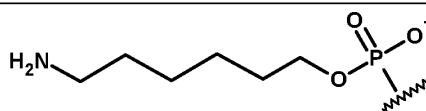
When positioned internally:



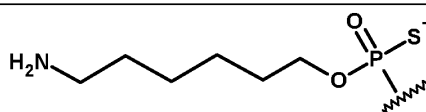
linkage towards 5' end

linkage towards 3' end

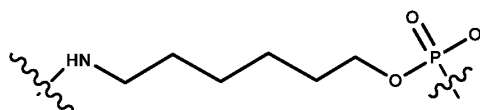
(6-SS-6)

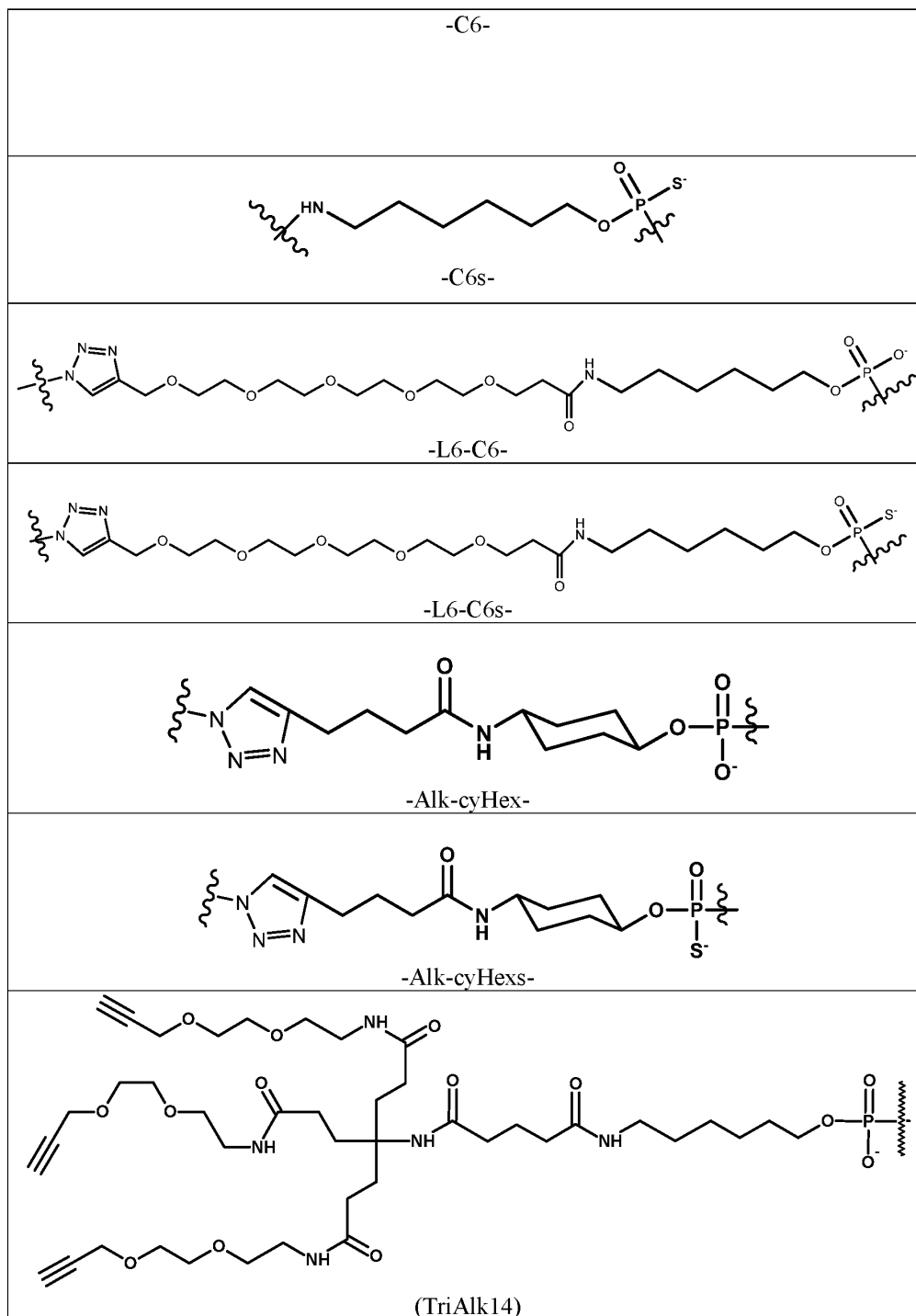


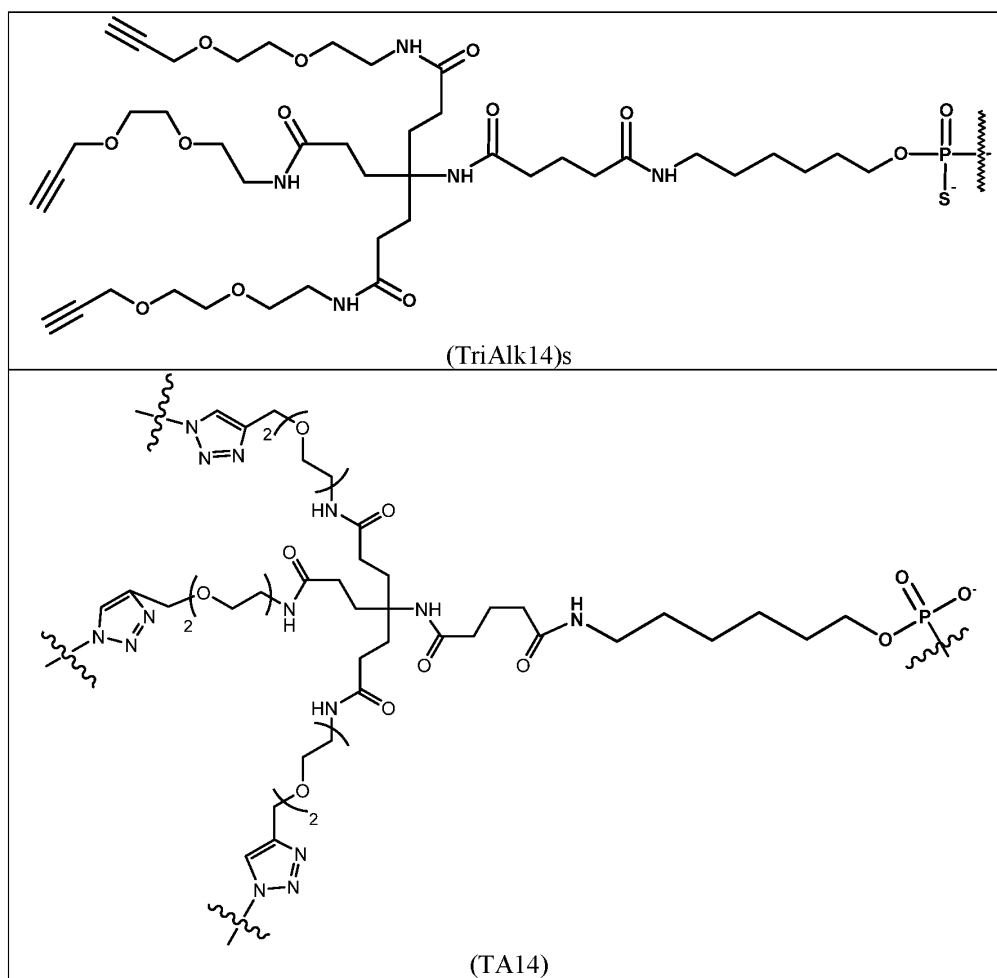
(NH2-C6)

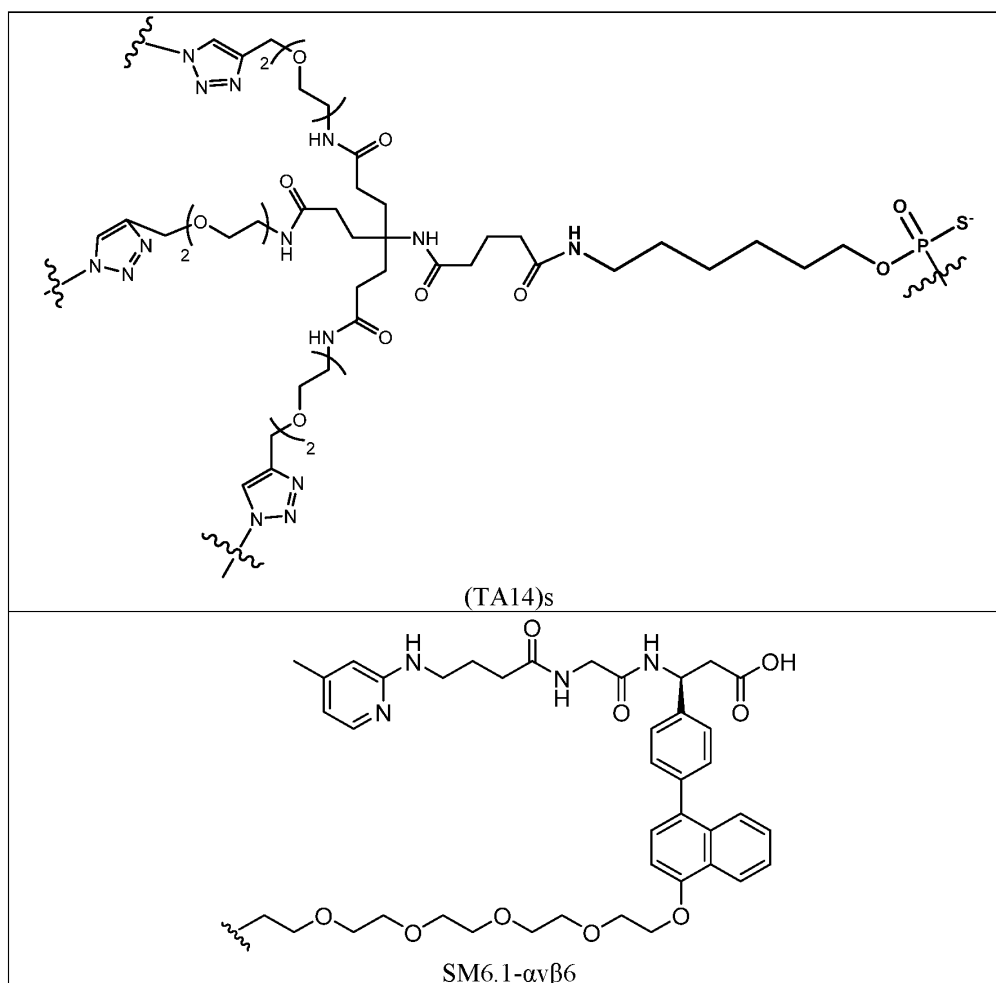


(NH2-C6)s









[0168] Alternatively, other linking groups known in the art may be used. In many instances, linking groups can be commercially acquired or alternatively, are incorporated into commercially available nucleotide phosphoramidites. (See, e.g., International Patent Application Publication No. WO 2019/161213, which is incorporated herein by reference in its entirety).

[0169] In some embodiments, a MUC5AC RNAi agent is delivered without being conjugated to a targeting ligand or pharmacokinetic/pharmacodynamic (PK/PD) modulator (referred to as being “naked” or a “naked RNAi agent”).

[0170] In some embodiments, a MUC5AC RNAi agent is conjugated to a targeting group, a linking group, a PK modulator, and/or another non-nucleotide group to facilitate delivery

of the MUC5AC RNAi agent to the cell or tissue of choice, for example, to an epithelial cell *in vivo*. In some embodiments, a MUC5AC RNAi agent is conjugated to a targeting group wherein the targeting group includes an integrin targeting ligand. In some embodiments, the integrin targeting ligand is an $\alpha\text{v}\beta 6$ integrin targeting ligand. In some embodiments, a targeting group includes one or more $\alpha\text{v}\beta 6$ integrin targeting ligands.

[0171] In some embodiments, a delivery vehicle may be used to deliver an RNAi agent to a cell or tissue. A delivery vehicle is a compound that improves delivery of the RNAi agent to a cell or tissue. A delivery vehicle can include, or consist of, but is not limited to: a polymer, such as an amphipathic polymer, a membrane active polymer, a peptide, a melittin peptide, a melittin-like peptide (MLP), a lipid, a reversibly modified polymer or peptide, or a reversibly modified membrane active polyamine.

[0172] In some embodiments, the RNAi agents can be combined with lipids, nanoparticles, polymers, liposomes, micelles, DPCs or other delivery systems available in the art for nucleic acid delivery. The RNAi agents can also be chemically conjugated to targeting groups, lipids (including, but not limited to cholesteryl and cholesteryl derivatives), encapsulating in nanoparticles, liposomes, micelles, conjugating to polymers or DPCs (see, for example WO 2000/053722, WO 2008/022309, WO 2011/104169, and WO 2012/083185, WO 2013/032829, WO 2013/158141, each of which is incorporated herein by reference), by iontophoresis, or by incorporation into other delivery vehicles or systems available in the art such as hydrogels, cyclodextrins, biodegradable nanocapsules, bioadhesive microspheres, or proteinaceous vectors. In some embodiments the RNAi agents can be conjugated to antibodies having affinity for pulmonary epithelial cells. In some embodiments, the RNAi agents can be linked to targeting ligands that have affinity for pulmonary epithelial cells or receptors present on pulmonary epithelial cells.

Pharmaceutical Compositions and Formulations

[0173] The MUC5AC RNAi agents disclosed herein can be prepared as pharmaceutical compositions or formulations (also referred to herein as “medicaments”). In some embodiments, pharmaceutical compositions include at least one MUC5AC RNAi agent. These pharmaceutical compositions are particularly useful in the inhibition of the expression of MUC5AC mRNA in a target cell, a group of cells, a tissue, or an organism. The pharmaceutical compositions can be used to treat a subject having a disease, disorder, or condition that would benefit from reduction in the level of the target mRNA, or inhibition

in expression of the target gene. The pharmaceutical compositions can be used to treat a subject at risk of developing a disease or disorder that would benefit from reduction of the level of the target mRNA or an inhibition in expression the target gene. In one embodiment, the method includes administering a MUC5AC RNAi agent linked to a targeting ligand as described herein, to a subject to be treated. In some embodiments, one or more pharmaceutically acceptable excipients (including vehicles, carriers, diluents, and/or delivery polymers) are added to the pharmaceutical compositions that include a MUC5AC RNAi agent, thereby forming a pharmaceutical formulation or medicament suitable for *in vivo* delivery to a subject, including a human.

[0174] The pharmaceutical compositions that include a MUC5AC RNAi agent and methods disclosed herein decrease the level of the target mRNA in a cell, group of cells, group of cells, tissue, organ, or subject, including by administering to the subject a therapeutically effective amount of a herein described MUC5AC RNAi agent, thereby inhibiting the expression of MUC5AC mRNA in the subject. In some embodiments, the subject has been previously identified or diagnosed as having a disease or disorder that can be mediated at least in part by a reduction in MUC5AC expression. In some embodiments, the subject has been previously diagnosed with having one or more mucoobstructive lung diseases, such as asthma, CF, COPD, NCFB, PCD. In some embodiments the mucoobstructive lung disease is severe asthma.

[0175] In some embodiments the subject has been previously diagnosed with having interstitial lung diseases, cancer (such as lung adenocarcinomas, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, ovarian cancer, and other tumors), respiratory infections (such as respiratory syncytial virus, influenza, rhinovirus), otitis media, inflammatory bowel disease, gallstone disease, allergic rhinitis, chronic rhinosinusitis or nasal polyposis.

[0176] Embodiments of the present disclosure include pharmaceutical compositions for delivering a MUC5AC RNAi agent to a pulmonary epithelial cell *in vivo*. Such pharmaceutical compositions can include, for example, a MUC5AC RNAi agent conjugated to a targeting group that comprises an integrin targeting ligand. In some embodiments, the integrin targeting ligand is comprised of an $\alpha\beta6$ integrin ligand.

[0177] In some embodiments, the described pharmaceutical compositions including a MUC5AC RNAi agent are used for treating or managing clinical presentations in a subject that would benefit from the inhibition of expression of MUC5AC. In some embodiments, a

therapeutically or prophylactically effective amount of one or more of pharmaceutical compositions is administered to a subject in need of such treatment. In some embodiments, administration of any of the disclosed MUC5AC RNAi agents can be used to decrease the number, severity, and/or frequency of symptoms of a disease in a subject.

[0178] In some embodiments, the described MUC5AC RNAi agents are optionally combined with one or more additional (i.e., second, third, etc.) therapeutics. A second therapeutic can be another MUC5AC RNAi agent (e.g., a MUC5AC RNAi agent that targets a different sequence within a MUC5AC gene). In some embodiments, a second therapeutic can be an RNAi agent that targets the MUC5AC gene. An additional therapeutic can also be a small molecule drug, antibody, antibody fragment, and/or aptamer. The MUC5AC RNAi agents, with or without the one or more additional therapeutics, can be combined with one or more excipients to form pharmaceutical compositions.

[0179] The described pharmaceutical compositions that include a MUC5AC RNAi agent can be used to treat at least one symptom in a subject having a disease or disorder that would benefit from reduction or inhibition in expression of MUC5AC mRNA. In some embodiments, the subject is administered a therapeutically effective amount of one or more pharmaceutical compositions that include a MUC5AC RNAi agent thereby treating the symptom. In other embodiments, the subject is administered a prophylactically effective amount of one or more MUC5AC RNAi agents, thereby preventing or inhibiting the at least one symptom.

[0180] In some embodiments, one or more of the described MUC5AC RNAi agents are administered to a mammal in a pharmaceutically acceptable carrier or diluent. In some embodiments, the mammal is a human.

[0181] The route of administration is the path by which a MUC5AC RNAi agent is brought into contact with the body. In general, methods of administering drugs, oligonucleotides, and nucleic acids, for treatment of a mammal are well known in the art and can be applied to administration of the compositions described herein. The MUC5AC RNAi agents disclosed herein can be administered via any suitable route in a preparation appropriately tailored to the particular route. Thus, in some embodiments, the herein described pharmaceutical compositions are administered via inhalation, intranasal administration, intratracheal administration, or oropharyngeal aspiration administration. In some embodiments, the pharmaceutical compositions can be administered by injection, for

example, intravenously, intramuscularly, intracutaneously, subcutaneously, intraarticularly, intraocularly, or intraperitoneally, or topically.

[0182] The pharmaceutical compositions including a MUC5AC RNAi agent described herein can be delivered to a cell, group of cells, tissue, or subject using oligonucleotide delivery technologies known in the art. In general, any suitable method recognized in the art for delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with the compositions described herein. For example, delivery can be by local administration, (e.g., direct injection, implantation, or topical administering), systemic administration, or subcutaneous, intravenous, intraperitoneal, or parenteral routes, including intracranial (e.g., intraventricular, intraparenchymal and intrathecal), intramuscular, transdermal, airway (aerosol), nasal, oral, rectal, or topical (including buccal and sublingual) administration. In some embodiments, the compositions are administered via inhalation, intranasal administration, oropharyngeal aspiration administration, or intratracheal administration. For example, in some embodiments, it is desired that the MUC5AC RNAi agents described herein inhibit the expression of an MUC5AC gene in the pulmonary epithelium, for which administration via inhalation (e.g., by an inhaler device, such as a metered-dose inhaler, or a nebulizer such as a jet or vibrating mesh nebulizer, or a soft mist inhaler) is particularly suitable and advantageous.

[0183] In some embodiments, the pharmaceutical compositions described herein comprise one or more pharmaceutically acceptable excipients. The pharmaceutical compositions described herein are formulated for administration to a subject.

[0184] As used herein, a pharmaceutical composition or medicament includes a pharmacologically effective amount of at least one of the described therapeutic compounds and one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients (excipients) are substances other than the Active Pharmaceutical Ingredient (API, therapeutic product, e.g., MUC5AC RNAi agent) that are intentionally included in the drug delivery system. Excipients do not exert or are not intended to exert a therapeutic effect at the intended dosage. Excipients can act to a) aid in processing of the drug delivery system during manufacture, b) protect, support or enhance stability, bioavailability or patient acceptability of the API, c) assist in product identification, and/or d) enhance any other attribute of the overall safety, effectiveness, of delivery of the API during storage or use. A pharmaceutically acceptable excipient may or may not be an inert substance.

[0185] Excipients include, but are not limited to: absorption enhancers, anti-adherents, anti-foaming agents, anti-oxidants, binders, buffering agents, carriers, coating agents, colors, delivery enhancers, delivery polymers, detergents, dextran, dextrose, diluents, disintegrants, emulsifiers, extenders, fillers, flavors, glidants, humectants, lubricants, oils, polymers, preservatives, saline, salts, solvents, sugars, surfactants, suspending agents, sustained release matrices, sweeteners, thickening agents, tonicity agents, vehicles, water-repelling agents, and wetting agents.

[0186] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water-soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor® ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0187] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0188] Formulations suitable for intra-articular administration can be in the form of a sterile aqueous preparation of the drug that can be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems can also be used to present the drug for both intra-articular and ophthalmic administration.

[0189] Formulations suitable for inhalation administration can be prepared by incorporating the active compound in the desired amount in an appropriate solvent, followed by sterile filtration. In general, formulations for inhalation administration are sterile solutions at physiological pH and have low viscosity (< 5 cP). Salts may be added to the formulation to balance tonicity. In some cases, surfactants or co-solvents can be added to increase active compound solubility and improve aerosol characteristics. In some cases, excipients can be added to control viscosity in order to ensure size and distribution of nebulized droplets.

[0190] In some embodiments, pharmaceutical formulations that include the MUC5AC RNAi agents disclosed herein suitable for inhalation administration can be prepared in water for injection (sterile water), isotonic saline (0.9% saline), or an aqueous sodium phosphate buffer (for example, the MUC5AC RNAi agent formulated in 0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic, in water).

[0191] The active compounds can be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0192] The MUC5AC RNAi agents can be formulated in compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the therapeutic effect to be achieved, and the

limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0193] A pharmaceutical composition can contain other additional components commonly found in pharmaceutical compositions. Such additional components include, but are not limited to: anti-pruritics, astringents, local anesthetics, or anti-inflammatory agents (e.g., antihistamine, diphenhydramine, etc.). It is also envisioned that cells, tissues, or isolated organs that express or comprise the herein defined RNAi agents may be used as “pharmaceutical compositions.” As used herein, “pharmacologically effective amount,” “therapeutically effective amount,” or simply “effective amount” refers to that amount of an RNAi agent to produce a pharmacological, therapeutic, or preventive result.

[0194] In some embodiments, the methods disclosed herein further comprise the step of administering a second therapeutic or treatment in addition to administering an RNAi agent disclosed herein. In some embodiments, the second therapeutic is another MUC5AC RNAi agent (e.g., a MUC5AC RNAi agent that targets a different sequence within the MUC5AC target). In other embodiments, the second therapeutic can be a small molecule drug, an antibody, an antibody fragment, and/or an aptamer.

[0195] In some embodiments, described herein are compositions that include a combination or cocktail of at least two MUC5AC RNAi agents having different sequences. In some embodiments, the two or more MUC5AC RNAi agents are each separately and independently linked to targeting groups. In some embodiments, the two or more MUC5AC RNAi agents are each linked to targeting groups that include or consist of integrin targeting ligands. In some embodiments, the two or more MUC5AC RNAi agents are each linked to targeting groups that include or consist of $\alpha\beta6$ integrin targeting ligands.

[0196] Described herein are compositions for delivery of MUC5AC RNAi agents to pulmonary epithelial cells. Furthermore, compositions for delivery of MUC5AC RNAi agents to cells, including renal epithelial cells and/or epithelial cells in the GI or reproductive tract and/or and ocular surface epithelial cells in the eye, *in vivo*, are generally described herein.

[0197] Generally, an effective amount of a MUC5AC RNAi agent disclosed herein will be in the range of from about 0.0001 to about 20 mg/kg of body weight/pulmonary deposited dose (PDD), e.g., from about 0.001 to about 5 mg/kg of body weight/pulmonary deposited dose. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 0.01 mg/kg to about 3.0 mg/kg of body weight per pulmonary deposited

dose. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 0.03 mg/kg to about 2.0 mg/kg of body weight per pulmonary deposited dose. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 0.01 to about 1.0 mg/kg of pulmonary deposited dose per body weight. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 0.25 to about 1.0 mg/kg of pulmonary deposited dose per body weight. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 0.25 mg/kg of pulmonary deposited dose per body weight. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 0.50 mg/kg of pulmonary deposited dose per body weight. In some embodiments, an effective amount of a MUC5AC RNAi agent will be in the range of from about 1.0 mg/kg of pulmonary deposited dose per body weight. Calculating the pulmonary deposited dose (PDD) is done in accordance with methods known in the art. (See Wolff R.K., Dorato M.A., *Toxicologic Testing of Inhaled Pharmaceutical Aerosols*, Crit Rev Toxicol., 1993; 23(4):343-369; Tepper *et al.*, International J. Toxicology, 2016, vol. 35(4):376-392). A comparable and alternatively acceptable method of calculating dose that is well known in the art, especially for human subjects, is determining the respirable delivered dose (RDD). RDD refers to the amount of drug contained in droplets of a size suitable for penetration into the lungs. Generally, an effective amount of a MUC5AC RNAi agent disclosed herein will be in the range of from about 0.001 to about 5 mg respirable delivered dose (RDD) / kg body weight.

[0198] For clinical applications, the amount of MUC5AC RNAi agent needed to be loaded into the delivery device of choice (e.g., a nebulizer) that is required to produce such RDDs in human subjects will depend upon the delivery device used (*see, for example*, Hatley RHM, Byrne SM, Variability in delivered dose and respirable delivered dose from nebulizers: are current regulatory testing guidelines sufficient to produce meaningful information?, Med Devices, 2017, 10:17-28). Some lower efficient nebulizers, for example, RDD is approximately 15%-25% of the dose loaded into the nebulizer. For other more efficient devices, for example, RDD is approximately 50%, approximately 60%, or even higher than 60% of the dose loaded into the nebulizer. In some embodiments, a fixed dose of, for example, approximately 5 mg, approximately 10 gm, approximately 20 mg, approximately 25 mg, approximately 50 mg, approximately 75 mg, approximately 100 mg, approximately 150 mg, approximately 200 mg, approximately 250 mg, or approximately

300 mg of MUC5AC RNAi agent may be loaded into the respective device of choice, which will produce an RDD from about 0.001 to about 5 mg / kg of body weight per dose. The amount desired or required to be administered will also likely depend on such variables as the overall health status of the patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipient in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered can be increased beyond the above upper level to rapidly achieve the desired blood-level or tissue-level, or the initial dosage can be smaller than the optimum. In various embodiments, a dose may be administered daily, weekly, bi-weekly, tri-weekly, once monthly, once quarterly (i.e. once every three months), or once every six months. In various embodiments, a dose may be administered at other intervals contained within the range provided above.

[0199] For treatment of disease or for formation of a medicament or composition for treatment of a disease, the pharmaceutical compositions described herein including a MUC5AC RNAi agent can be combined with an excipient or with a second therapeutic agent or treatment including, but not limited to: a second or other RNAi agent, a small molecule drug, an antibody, an antibody fragment, peptide, and/or an aptamer.

[0200] The described MUC5AC RNAi agents, when added to pharmaceutically acceptable excipients or adjuvants, can be packaged into kits, containers, packs, or dispensers. The pharmaceutical compositions described herein can be packaged in dry powder or aerosol inhalers, other metered-dose inhalers, nebulizers, pre-filled syringes, or vials.

Methods of Treatment and Inhibition of MUC5AC Expression

[0201] The MUC5AC RNAi agents disclosed herein can be used to treat a subject (e.g., a human or other mammal) having a disease or disorder that would benefit from administration of the RNAi agent. In some embodiments, the RNAi agents disclosed herein can be used to treat a subject (e.g., a human) that would benefit from a reduction and/or inhibition in expression of MUC5AC mRNA and/or a reduction in MUC5AC receptor levels.

[0202] In some embodiments, the RNAi agents disclosed herein can be used to treat a subject (e.g., a human) having a disease or disorder for which the subject would benefit from reduction in MUC5AC receptors, including but not limited to, mucoobstructive lung diseases (such as asthma, CF, COPD, NCFB, PCD), allergic bronchopulmonary

aspergillosis, interstitial lung diseases, cancer (such as lung adenocarcinomas, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, ovarian cancer, and other tumors), respiratory infections (such as respiratory syncytial virus, influenza, rhinovirus), otitis media, inflammatory bowel disease, gallstone disease, allergic rhinitis, chronic rhinosinusitis and nasal polyposis. In some embodiments the pulmonary diseases is severe asthma. Treatment of a subject can include therapeutic and/or prophylactic treatment. The subject is administered a therapeutically effective amount of any one or more MUC5AC RNAi agents described herein. The subject can be a human, patient, or human patient. The subject may be an adult, adolescent, child, or infant. Administration of a pharmaceutical composition described herein can be to a human being or animal.

[0203] Increased membrane MUC5AC activity is known to promote mucocoobstruction tissues. In some embodiments, the described MUC5AC RNAi agents are used to treat at least one symptom mediated at least in part by a reduction in MUC5AC levels, in a subject. The subject is administered a therapeutically effective amount of any one or more of the described MUC5AC RNAi agents. In some embodiments, the subject is administered a prophylactically effective amount of any one or more of the described RNAi agents, thereby treating the subject by preventing or inhibiting the at least one symptom.

[0204] In certain embodiments, the present disclosure provides methods for treatment of diseases, disorders, conditions, or pathological states mediated at least in part by MUC5AC gene expression, in a patient in need thereof, wherein the methods include administering to the patient any of the MUC5AC RNAi agents described herein.

[0205] In some embodiments, the MUC5AC RNAi agents are used to treat or manage a clinical presentation or pathological state in a subject, wherein the clinical presentation or pathological state is mediated at least in part by a reduction in MUC5AC expression. The subject is administered a therapeutically effective amount of one or more of the MUC5AC RNAi agents or MUC5AC RNAi agent-containing compositions described herein. In some embodiments, the method comprises administering a composition comprising a MUC5AC RNAi agent described herein to a subject to be treated.

[0206] In a further aspect, the disclosure features methods of treatment (including prophylactic or preventative treatment) of diseases or symptoms that may be addressed by a reduction in MUC5AC receptor levels, the methods comprising administering to a subject in need thereof a MUC5AC RNAi agent that includes an antisense strand comprising the

sequence of any of the sequences in Table 2, Table 3, or Table 11. Also described herein are compositions for use in such methods.

[0207] The described MUC5AC RNAi agents and/or compositions that include MUC5AC RNAi agents can be used in methods for therapeutic treatment of disease or conditions caused by enhanced or elevated MUC5AC protein or MUC5AC gene expression. Such methods include administration of a MUC5AC RNAi agent as described herein to a subject, e.g., a human or animal subject.

[0208] In another aspect, the disclosure provides methods for the treatment (including prophylactic treatment) of a pathological state (such as a condition or disease) mediated at least in part by MUC5AC expression, wherein the methods include administering to a subject a therapeutically effective amount of an RNAi agent that includes an antisense strand comprising the sequence of any of the sequences in Table 2, Table 3, or Table 11.

[0209] In some embodiments, methods for inhibiting expression of an MUC5AC gene are disclosed herein, wherein the methods include administering to a cell an RNAi agent that includes an antisense strand comprising the sequence of any of the sequences in Table 2, Table 3, or Table 11.

[0210] In some embodiments, methods for the treatment (including prophylactic treatment) of a pathological state mediated at least in part by MUC5AC expression are disclosed herein, wherein the methods include administering to a subject a therapeutically effective amount of an RNAi agent that includes a sense strand comprising the sequence of any of the sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0211] In some embodiments, methods for inhibiting expression of an MUC5AC gene are disclosed herein, wherein the methods comprise administering to a cell an RNAi agent that includes a sense strand comprising the sequence of any of the sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0212] In some embodiments, methods for the treatment (including prophylactic treatment) of a pathological state mediated at least in part by MUC5AC expression are disclosed herein, wherein the methods include administering to a subject a therapeutically effective amount of an RNAi agent that includes a sense strand comprising the sequence of any of the sequences in Table 4, Table 5, Table 6, Table 7, or Table 11, and an antisense strand comprising the sequence of any of the sequences in Table 3 or Table 11.

[0213] In some embodiments, methods for inhibiting expression of a MUC5AC gene are disclosed herein, wherein the methods include administering to a cell an RNAi agent that

includes a sense strand comprising the sequence of any of the sequences in Table 4, Table 5, Table 6, Table 7, or Table 11, and an antisense strand comprising the sequence of any of the sequences in Table 3 or Table 11.

[0214] In some embodiments, methods of inhibiting expression of a MUC5AC gene are disclosed herein, wherein the methods include administering to a subject a MUC5AC RNAi agent that includes a sense strand consisting of the nucleobase sequence of any of the sequences in Table 4, Table 5, Table 6, Table 7, or Table 11, and the antisense strand consisting of the nucleobase sequence of any of the sequences in Table 3 or Table 11. In other embodiments, disclosed herein are methods of inhibiting expression of a MUC5AC gene, wherein the methods include administering to a subject a MUC5AC RNAi agent that includes a sense strand consisting of the modified sequence of any of the modified sequences in Table 4, Table 5, Table 6, Table 7, or Table 11, and the antisense strand consisting of the modified sequence of any of the modified sequences in Table 3 or Table 11.

[0215] In some embodiments, methods for inhibiting expression of an MUC5AC gene in a cell are disclosed herein, wherein the methods include administering one or more MUC5AC RNAi agents comprising a duplex structure of one of the duplexes set forth in Tables 8A, 8B, 8C, 9, 10A, 10B, and 11.

[0216] In some embodiments, the quantity or amount of MUC5AC protein and/or MUC5AC mRNA in certain pulmonary epithelial cells of subject to whom a described MUC5AC RNAi agent is administered is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or greater than 99%, relative to the subject prior to being administered the MUC5AC RNAi agent or to a subject not receiving the MUC5AC RNAi agent. In some embodiments, MUC5AC protein levels in certain epithelial cells of a subject to whom a described MUC5AC RNAi agent is administered is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or greater than 99%, relative to the subject prior to being administered the MUC5AC RNAi agent or to a subject not receiving the MUC5AC RNAi agent. The gene expression level, protein level, and/or mRNA level in the subject may be reduced in a cell, group of cells, and/or tissue of the subject. In some embodiments, the MUC5AC mRNA levels in certain epithelial cells subject to whom a described MUC5AC RNAi agent has been administered is reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 98% relative to the subject prior to

being administered the MUC5AC RNAi agent or to a subject not receiving the MUC5AC RNAi agent.

[0217] A reduction in MUC5AC mRNA and MUC5AC protein levels can be assessed by any methods known in the art. Reduction or decrease in MUC5AC mRNA and/or MUC5AC protein levels are collectively referred to herein as a decrease in, reduction of, or inhibition of MUC5AC gene expression. The Examples set forth herein illustrate known methods for assessing inhibition of MUC5AC.

Cells, Tissues, Organs, and Non-Human Organisms

[0218] Cells, tissues, organs, and non-human organisms that include at least one of the MUC5AC RNAi agents described herein are contemplated. The cell, tissue, organ, or non-human organism is made by delivering the RNAi agent to the cell, tissue, organ, or non-human organism.

Additional Illustrative Embodiments

[0219] Provided here are certain additional illustrative embodiments of the disclosed technology. These embodiments are illustrative only and do not limit the scope of the present disclosure or of the claims attached hereto.

[0220] Embodiment 1. An RNAi agent for inhibiting expression of a Mucin 5AC gene, comprising: an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2 or Table 3; and a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand

[0221] Embodiment 2. The RNAi agent of Embodiment 1, wherein the antisense strand comprises nucleotides 2-18 of any one of the sequences provided in Table 2 or Table 3.

[0222] Embodiment 3. The RNAi agent of Embodiment 1 or Embodiment 2, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2 or Table 4, and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.

[0223] Embodiment 4. The RNAi agent of any one of Embodiments 1-3, wherein at least one nucleotide of the RNAi agent is a modified nucleotide or includes a modified internucleoside linkage.

[0224] Embodiment 5. The RNAi agent of any one of Embodiments 1-4, wherein all or substantially all of the nucleotides are modified nucleotides.

[0225] Embodiment 6. The RNAi agent of any one of Embodiments 4-5, wherein the modified nucleotide is selected from the group consisting of: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2',3'-seco nucleotide mimic, locked nucleotide, 2'-F-arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted 2'-O-methyl nucleotide, inverted 2'-deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, vinyl phosphonate-containing nucleotide, cyclopropyl phosphonate-containing nucleotide, and 3'-O-methyl nucleotide.

[0226] Embodiment 7. The RNAi agent of Embodiment 5, wherein all or substantially all of the nucleotides are modified with 2'-O-methyl nucleotides, 2'-fluoro nucleotides, or combinations thereof

[0227] Embodiment 8. The RNAi agent of any one of Embodiments 1-7, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3 or Table 11.

[0228] Embodiment 9. The RNAi agent of any one of Embodiments 1-8, wherein the sense strand comprises the nucleotide sequence of any one of the modified sense strand sequences provided in Table 4 or Table 11.

[0229] Embodiment 10. The RNAi agent of Embodiment 1, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3 or Table 11, and the sense strand comprises the nucleotide sequence of any one of the modified sense strand sequences provided in Table 4 or Table 11.

[0230] Embodiment 11. The RNAi agent of any one of Embodiments 1-10, wherein the sense strand is between 18 and 30 nucleotides in length, and the antisense strand is between 18 and 30 nucleotides in length.

[0231] Embodiment 12. The RNAi agent of Embodiment 11, wherein the sense strand and the antisense strand are each between 18 and 27 nucleotides in length.

[0232] Embodiment 13. The RNAi agent of Embodiment 12, wherein the sense strand and the antisense strand are each between 18 and 24 nucleotides in length.

[0233] Embodiment 14. The RNAi agent of Embodiment 13, wherein the sense strand and the antisense strand are each 21 nucleotides in length.

[0234] Embodiment 15. The RNAi agent of Embodiment 14, wherein the RNAi agent has two blunt ends.

[0235] Embodiment 16. The RNAi agent of any one of Embodiments 1-15, wherein the sense strand comprises one or two terminal caps.

[0236] Embodiment 17. The RNAi agent of any one of Embodiments 1-16, wherein the sense strand comprises one or two inverted abasic residues.

[0237] Embodiment 18. The RNAi agent of Embodiment 1, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex having the structure of any one of the duplexes in Table 8A, Table 8B, Table 8C, Table 9, Table 10A, or Table 10B.

[0238] Embodiment 19. The RNAi agent of Embodiment 18, wherein all or substantially all of the nucleotides are modified nucleotides.

[0239] Embodiment 20. The RNAi agent of Embodiment 1, wherein the antisense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); or

UUCUUGUUCAGGCAAUAUCA (SEQ ID NO:83).

[0240] Embodiment 21. The RNAi agent of Embodiment 1, wherein the antisense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACAGC (SEQ ID NO:1525); or

UUCUUGUUCAGGCAAUCAGC (SEQ ID NO:1535).

[0241] Embodiment 22. The RNAi agent of Embodiment 1, wherein the sense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UGUUCUGCGACUACUACAA (SEQ ID NO:568); or

UGAUUUGCCUGAACAAGAA (SEQ ID NO:572).

[0242] Embodiment 23. The RNAi agent of Embodiment 20, 21, or 22, wherein all or substantially all of the nucleotides are modified nucleotides

[0243] Embodiment 24. The RNAi agent of Embodiment 1, wherein the antisense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127);

usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1065);

usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166); or

cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191);

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

[0244] Embodiment 25. The RNAi agent of Embodiment 1, wherein the sense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

gscuguucuGfCfGfacuacuacaa (SEQ ID NO:1265); or

gscugauUfuGfcCfugaacaagaa (SEQ ID NO:1315);

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

[0245] Embodiment 26. The RNAi agent of any one of Embodiments 20-25, wherein the sense strand further includes inverted abasic residues at the 3' terminal end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both.

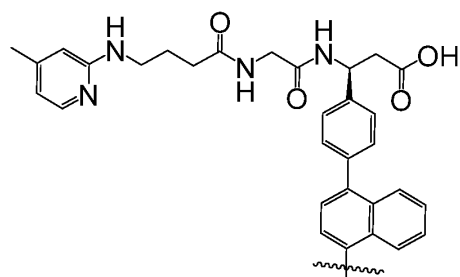
[0246] Embodiment 27. The RNAi agent of any one of Embodiments 1-26, wherein the RNAi agent is linked to a targeting ligand.

[0247] Embodiment 28. The RNAi agent of Embodiment 27, wherein the targeting ligand has affinity for a cell receptor expressed on an epithelial cell.

[0248] Embodiment 29. The RNAi agent of Embodiment 28, wherein the targeting ligand comprises an integrin targeting ligand.

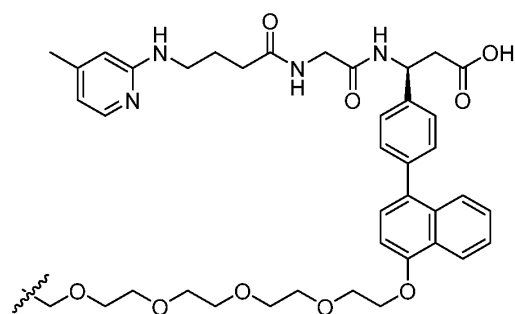
[0249] Embodiment 30. The RNAi agent of Embodiment 29, wherein the integrin targeting ligand is an $\alpha\beta6$ integrin targeting ligand.

[0250] Embodiment 31. The RNAi agent of Embodiment 30, wherein the targeting ligand comprises the structure:



or a pharmaceutically acceptable salt

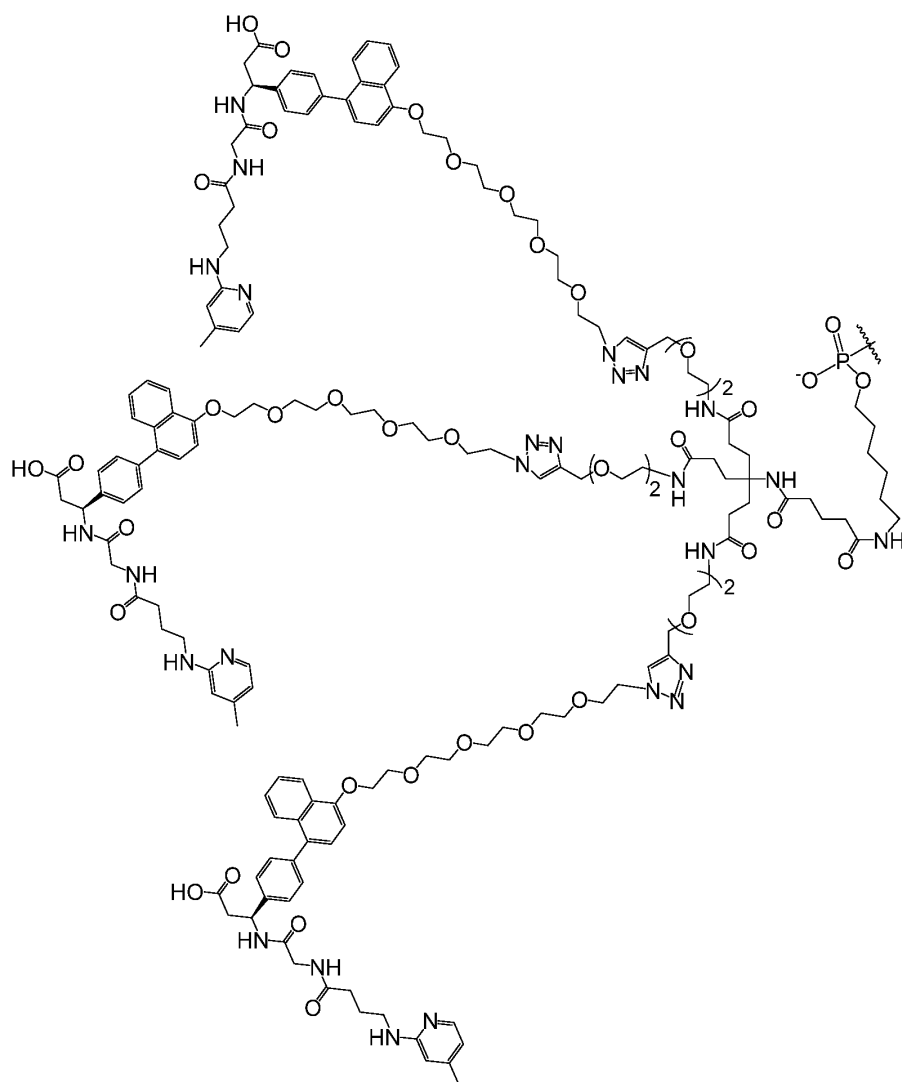
thereof, or



or a pharmaceutically acceptable salt

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

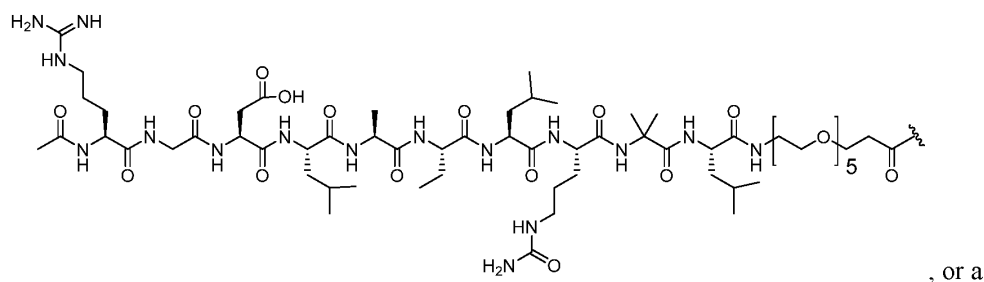
[0251] Embodiment 32. The RNAi agent of any one of Embodiments 27-30, wherein RNAi agent is conjugated to a targeting ligand having the following structure:



, or a

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

[0252] Embodiment 33. The RNAi agent of any one of Embodiments 27-30, wherein the targeting ligand has the following structure:



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

[0253] Embodiment 34. The RNAi agent of any one of Embodiments 27-33, wherein the targeting ligand is conjugated to the sense strand.

[0254] Embodiment 35. The RNAi agent of Embodiment 34, wherein the targeting ligand is conjugated to the 5' terminal end of the sense strand.

[0255] Embodiment 36. A composition comprising the RNAi agent of any one of Embodiments 1-35, wherein the composition further comprises a pharmaceutically acceptable excipient.

[0256] Embodiment 37. The composition of Embodiment 36, further comprising a second RNAi agent capable of inhibiting the expression of Mucin 5AC gene expression.

[0257] Embodiment 38. The composition of any one of Embodiments 36-37, further comprising one or more additional therapeutics.

[0258] Embodiment 39. The composition of any one of Embodiments 36-38, wherein the composition is formulated for administration by inhalation.

[0259] Embodiment 40. The composition of Embodiment 39, wherein the composition is delivered by a metered-dose inhaler, jet nebulizer, vibrating mesh nebulizer, or soft mist inhaler.

[0260] Embodiment 41. The composition of any of Embodiments 36-40, wherein the RNAi agent is a sodium salt.

[0261] Embodiment 42. The composition of any of Embodiments 36-41, wherein the pharmaceutically acceptable excipient is water for injection.

[0262] Embodiment 43. The composition of any of Embodiments 36-42, wherein the pharmaceutically acceptable excipient is isotonic saline.

[0263] Embodiment 44. A method for inhibiting expression of a MUC5AC gene in a cell, the method comprising introducing into a cell an effective amount of an RNAi agent of any one of Embodiments 1-35 or the composition of any one of Embodiments 36-43.

[0264] Embodiment 45. The method of Embodiment 44, wherein the cell is within a subject.

[0265] Embodiment 46. The method of Embodiment 45, wherein the subject is a human subject.

[0266] Embodiment 47. The method of any one of claims 44-46, wherein following the administration of the RNAi agent the Mucin 5AC gene expression is inhibited by at least about 30%.

[0267] Embodiment 48. A method of treating one or more symptoms or diseases associated with MUC5AC protein levels, the method comprising administering to a human subject in need thereof a therapeutically effective amount of the composition of any one of Embodiments 36-43.

[0268] Embodiment 49. The method of Embodiment 48, wherein the disease is a mucoobstructive lung disease.

[0269] Embodiment 50. The method of Embodiment 49, wherein the mucoobstructive lung disease is asthma (including severe asthma), cystic fibrosis (CF), bronchiectasis (NCFB), or chronic obstructive pulmonary disease (COPD).

[0270] Embodiment 51. The method of Embodiment 50, wherein the disease is asthma (including severe asthma).

[0271] Embodiment 52. The method of Embodiment 48, wherein the disease is cancer.

[0272] Embodiment 53. The method of Embodiment 52, wherein the cancer is lung adenocarcinoma, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, or ovarian cancer.

[0273] Embodiment 54. The method of any one of Embodiments 44-53, wherein the RNAi agent is administered at a pulmonary deposited dose (PDD) of about 0.01 mg/kg to about 5.0 mg/kg of body weight of the subject.

[0274] Embodiment 55. The method of any one of Embodiments 44-53, wherein the RNAi agent is administered at a pulmonary deposited dose (PDD) of about 0.1 mg/kg to about 2.0 mg/kg of body weight of the subject.

[0275] Embodiment 56. The method of any one of Embodiments 44-53, wherein the RNAi agent is administered at a respirable delivered dose (RDD) of about 0.01 mg/kg to about 5.0 mg/kg of body weight of the subject.

[0276] Embodiment 57. The method of any one of Embodiments 44-53, wherein the RNAi agent is administered at a respirable delivered dose (RDD) of about 0.1 mg/kg to about 2.0 mg/kg of body weight of the subject.

[0277] Embodiment 58. The method of any of Embodiments 44-57, wherein the RNAi agent is administered in two or more doses.

[0278] Embodiment 59. Use of the RNAi agent of any one of Embodiments 1-35, for the treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC protein levels.

[0279] Embodiment 60. Use of the composition according to any one of Embodiments 36-43, for the treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC gene expression.

[0280] Embodiment 61. Use of the composition according to any one of Embodiments 36-43, for the manufacture of a medicament for treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC gene expression.

[0281] Embodiment 62. The use of any one of Embodiments 59-61, wherein the disease is asthma (including severe asthma).

[0282] Embodiment 63. A method of making an RNAi agent of any one of Embodiments 1-35, comprising annealing a sense strand and an antisense strand to form a double-stranded ribonucleic acid molecule.

[0283] Embodiment 64. The method of Embodiment 63, wherein the sense strand comprises a targeting ligand.

[0284] Embodiment 65. The method of Embodiment 64, comprising conjugating a targeting ligand to the sense strand.

[0285] Embodiment 66. An RNAi agent for inhibiting expression of a Mucin 5AC gene, comprising:

an antisense strand comprising at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from any one of the sequences provided in Table 2, Table 3, or Table 11; and a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.

[0286] Embodiment 67. An RNAi agent for inhibiting expression of a Mucin 5AC (MUC5AC) gene, comprising:

an antisense strand comprising at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from any one of the sequences disclosed in Table 2 or Table 3; and a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.

[0287] Embodiment 68. An RNAi agent for inhibiting expression of a Mucin 5AC (MUC5AC) gene, comprising:

a sense strand comprising at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from a stretch of the same length of nucleotides of SEQ ID NO:1; and an antisense strand comprising a nucleotide sequence that is at least partially complementary to the sense strand.

[0288] Embodiment 69. An inhibitor of a MUC5AC gene comprising an antisense nucleotide sequence having at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides that are complementary to any of the target nucleotide sequences in Table 1.

[0289] Embodiment 70. An RNAi agent comprising (i) an antisense strand comprising a nucleotide sequence having at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from any of the nucleotide sequences in Table 2, Table 3 or Table 11, and (ii) a sense strand at least partially complementary to the antisense strand.

[0290] Embodiment 71. An RNAi agent comprising (i) an antisense strand comprising, consisting of, or consisting essentially of a nucleotide sequence from any of the antisense strand nucleotide sequences in Table 2, Table 3 or Table 11, and (ii) a sense strand comprising, consisting of, or consisting essentially of a nucleotide sequence from any of the sense strand nucleotide sequences in Table 2, Table 4, Table 5, Table 6, Table 7, or Table 11.

[0291] Embodiment 72. An RNAi agent comprising an antisense strand and sense strand annealed to form a duplex, wherein the duplex has the structure of any of the duplexes set forth in Table 8A, Table 8B, Table 8C, Table 9, Table 10, or Table 11.

[0292] Embodiment 73. An RNAi agent for inhibiting expression of a Mucin 5AC gene, comprising:

an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2 or Table 3; and

a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand, wherein optionally all or substantially all of the nucleotides of the sense strand and the antisense strand modified nucleotides, and wherein the sense strand is optionally linked to a targeting ligand.

[0293] The above provided embodiments and items are now illustrated with the following, non-limiting examples.

EXAMPLES

Example 1. Synthesis of MUC5AC RNAi Agents.

[0294] MUC5AC RNAi agent duplexes disclosed herein were synthesized in accordance with the following:

[0295] *A. Synthesis.* The sense and antisense strands of the MUC5AC RNAi agents were synthesized according to phosphoramidite technology on solid phase used in oligonucleotide synthesis. Depending on the scale, a MerMade96E® (Bioautomation), a MerMade12® (Bioautomation), or an OP Pilot 100 (GE Healthcare) was used. Syntheses were performed on a solid support made of controlled pore glass (CPG, 500 Å or 600Å, obtained from Prime Synthesis, Aston, PA, USA). All RNA and 2'-modified RNA phosphoramidites were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA). Specifically, the 2'-O-methyl phosphoramidites that were used included the following: (5'-O-dimethoxytrityl-N⁶-(benzoyl)-2'-O-methyl-adenosine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, 5'-O-dimethoxy-trityl-N⁴-(acetyl)-2'-O-methyl-cytidine-3'-O-(2-cyanoethyl-N,N-diisopropyl-amino) phosphoramidite, (5'-O-dimethoxytrityl-N²-(isobutyryl)-2'-O-methyl-guanosine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, and 5'-O-dimethoxytrityl-2'-O-methyl-uridine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite. The 2'-deoxy-2'-fluoro-phosphoramidites carried the same protecting groups as the 2'-O-methyl RNA amidites. 5'-dimethoxytrityl-2'-O-methyl-inosine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidites were purchased from Glen Research (Virginia). The inverted abasic (3'-O-dimethoxytrityl-2'-deoxyribose-5'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidites were purchased from ChemGenes (Wilmington, MA, USA). The following UNA phosphoramidites were used: 5'-(4,4'-Dimethoxytrityl)-N⁶-(benzoyl)-2',3'-seco-adenosine, 2'-benzoyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-Dimethoxytrityl)-N-acetyl-2',3'-seco-cytosine, 2'-benzoyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-Dimethoxytrityl)-N-isobutyryl-2',3'-seco-guanosine, 2'-benzoyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, and 5'-(4,4'-Dimethoxy-trityl)-2',3'-seco-uridine, 2'-benzoyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite. TFA aminolink phosphoramidites were also commercially purchased (ThermoFisher). Linker L6 was purchased as propargyl-PEG5-NHS from BroadPharm (catalog # BP-20907) and coupled to the NH₂-C₆ group from an aminolink phosphoramidite to form -L6-C₆-, using standard coupling conditions. The linker Alk-

cyHex was similarly commercially purchased from Lumiprobe (alkyne phosphoramidite, 5'-terminal) as a propargyl-containing compound phosphoramidite compound to form the linker -Alk-cyHex-. In each case, phosphorothioate linkages were introduced as specified using the conditions set forth herein. The cyclopropyl phosphonate phosphoramidites were synthesized in accordance with International Patent Application Publication No. WO 2017/214112 (see also Altenhofer et. al., Chem. Communications (Royal Soc. Chem.), 57(55):6808-6811 (2021)).

[0296] Tri-alkyne-containing phosphoramidites were dissolved in anhydrous dichloromethane or anhydrous acetonitrile (50 mM), while all other amidites were dissolved in anhydrous acetonitrile (50 mM) and molecular sieves (3Å) were added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 10 minutes (RNA), 90 seconds (2' O-Me), and 60 seconds (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, MA, USA) in anhydrous acetonitrile was employed.

[0297] Alternatively, tri-alkyne moieties were introduced post-synthetically (see section E, below). For this route, the sense strand was functionalized with a 5' and/or 3' terminal nucleotide containing a primary amine. TFA aminolink phosphoramidite was dissolved in anhydrous acetonitrile (50 mM) and molecular sieves (3Å) were added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 10 minutes (RNA), 90 seconds (2' O-Me), and 60 seconds (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, MA, USA) in anhydrous acetonitrile was employed.

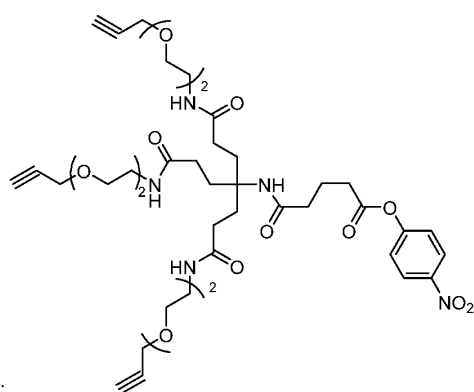
[0298] *B. Cleavage and deprotection of support bound oligomer.* After finalization of the solid phase synthesis, the dried solid support was treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% to 31% ammonium hydroxide solution (Aldrich) for 1.5 hours at 30°C. The solution was evaporated and the solid residue was reconstituted in water (see below).

[0299] *C. Purification.* Crude oligomers were purified by anionic exchange HPLC using a TSKgel SuperQ-5PW 13µm column and Shimadzu LC-8 system. Buffer A was 20 mM Tris, 5 mM EDTA, pH 9.0 and contained 20% Acetonitrile and buffer B was the same

as buffer A with the addition of 1.5 M sodium chloride. UV traces at 260 nm were recorded. Appropriate fractions were pooled then run on size exclusion HPLC using a GE Healthcare XK 16/40 column packed with Sephadex G-25 fine with a running buffer of 100mM ammonium bicarbonate, pH 6.7 and 20% Acetonitrile or filtered water. Alternatively, pooled fractions were desalted and exchanged into an appropriate buffer or solvent system via tangential flow filtration.

[0300] *D. Annealing.* Complementary strands were mixed by combining equimolar RNA solutions (sense and antisense) in 1× PBS (Phosphate-Buffered Saline, 1×, Corning, Cellgro) to form the RNAi agents. Some RNAi agents were lyophilized and stored at −15 to −25°C. Duplex concentration was determined by measuring the solution absorbance on a UV-Vis spectrometer in 1× PBS. The solution absorbance at 260 nm was then multiplied by a conversion factor (0.050 mg/(mL·cm)) and the dilution factor to determine the duplex concentration.

[0301] *E. Conjugation of Tri-alkyne linker.* In some embodiments a tri-alkyne linker is conjugated to the sense strand of the RNAi agent on resin as a phosphoramidite (*see* Example 1G for the synthesis of an example tri-alkyne linker phosphoramidite and Example 1A for the conjugation of the phosphoramidite.). In other embodiments, a tri-alkyne linker may be conjugated to the sense strand following cleavage from the resin, described as follows: either prior to or after annealing, in some embodiments, the 5' or 3' amine functionalized sense strand is conjugated to a tri-alkyne linker. An example tri-alkyne linker structure that can be used in forming the constructs disclosed herein is as



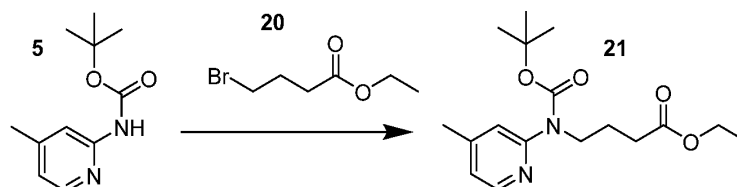
follows:

To conjugate the tri-alkyne linker to the annealed duplex, amine-functionalized duplex was dissolved in 90% DMSO/10% H₂O, at ~50-70 mg/mL. 40 equivalents triethylamine was added, followed by 3

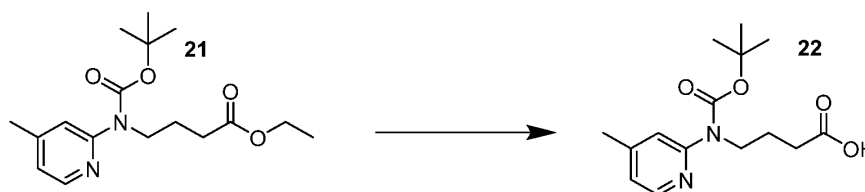
equivalents tri-alkyne-PNP. Once complete, the conjugate was precipitated twice in a solvent system of 1x phosphate buffered saline/acetonitrile (1:14 ratio), and dried.

[0302] F. *Synthesis of Targeting Ligand SM6.1*

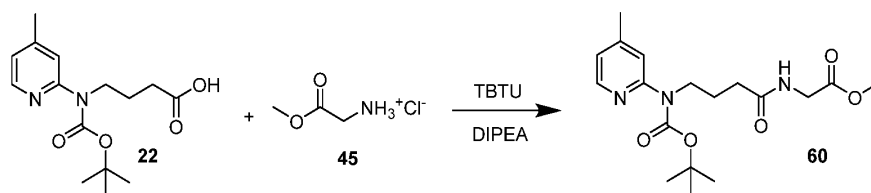
((S)-3-(4-(4-((14-azido-3,6,9,12-tetraoxatetradecyl)oxy)naphthalen-1-yl)phenyl)-3-(2-(4-((4-methylpyridin-2-yl)amino)butanamido)acetamido)propanoic acid)



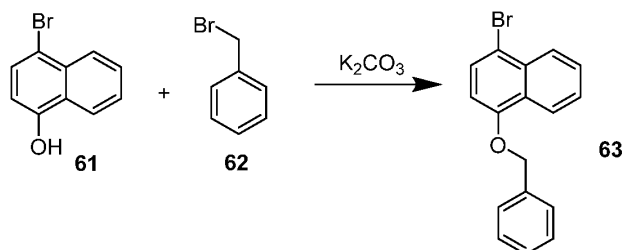
[0303] Compound 5 (tert-Butyl(4-methylpyridin-2-yl)carbamate) (0.501 g, 2.406 mmol, 1 equiv.) was dissolved in DMF (17 mL). To the mixture was added NaH (0.116 mg, 3.01 mmol, 1.25 eq, 60 % dispersion in oil) The mixture stirred for 10 min before adding Compound 20 (Ethyl 4-Bromobutyrate (0.745 g, 3.82 mmol, 0.547 mL)) (Sigma 167118). After 3 hours the reaction was quenched with ethanol (18 mL) and concentrated. The concentrate was dissolved in DCM (50 mL) and washed with saturated aq. NaCl solution (1 x 50 mL), dried over Na₂SO₄, filtered and concentrated. The product was purified on silica column, gradient 0-5% Methanol in DCM.



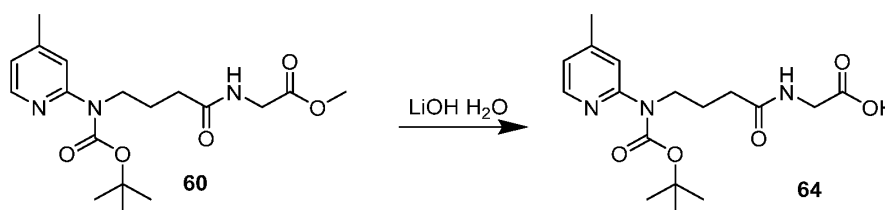
[0304] Compound 21 was dissolved (0.80 g, 2.378 mmol) in 100 mL of Acetone : 0.1 M NaOH [1:1]. The reaction was monitored by TLC (5% ethyl acetate in hexane). The organics were concentrated away, and the residue was acidified to pH 3-4 with 0.3 M Citric Acid (40 mL). The product was extracted with DCM (3 x 75 mL). The organics were pooled, dried over Na₂SO₄, filtered and concentrated. The product was used without further purification.



[0305] To a solution of Compound 22 (1.1 g, 3.95 mmol, 1 equiv.), Compound 45 (595 mg, 4.74 mmol, 1.2 equiv.), and TBTU (1.52 g, 4.74 mmol, 1.2 equiv.) in anhydrous DMF (10 mL) was added diisopropylethylamine (2.06 mL, 11.85 mmol, 3 equiv.) at 0 °C. The reaction mixture was warmed to room temperature and stirred 3 hours. The reaction was quenched by saturated NaHCO₃ solution (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic phase was combined, dried over anhydrous Na₂SO₄, and concentrated. The product was separated by CombiFlash® using silica gel as the stationary phase. LC-MS: calculated [M+H]⁺ 366.20, found 367.

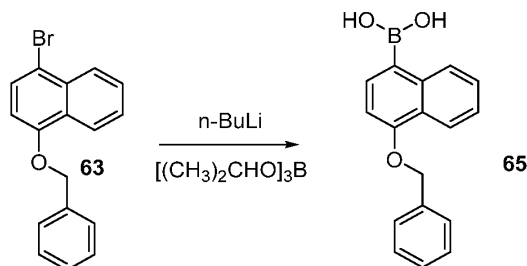


[0306] To a solution of compound 61 (2 g, 8.96 mmol, 1 equiv.), and compound 62 (2.13 mL, 17.93 mmol, 2 equiv.) in anhydrous DMF (10 mL) was added K₂CO₃ (2.48 g, 17.93 mmol, 2 equiv.) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic phase was combined, dried over anhydrous Na₂SO₄, and concentrated. The product was separated by CombiFlash® using silica gel as the stationary phase.

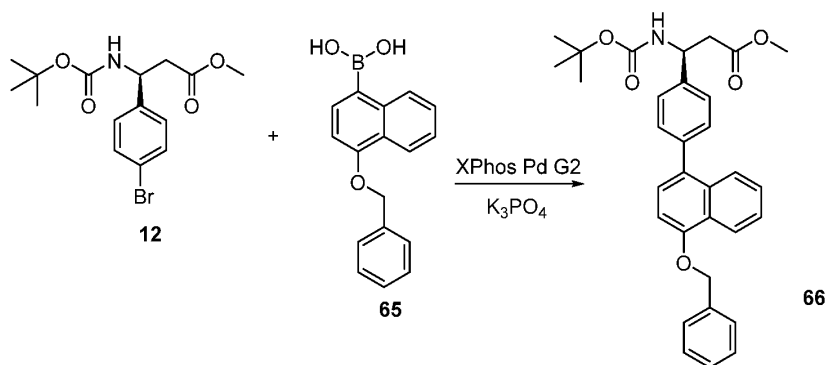


[0307] To a solution of compound 60 (1.77 g, 4.84 mmol, 1 equiv.) in THF (5 mL) and H₂O (5 mL) was added lithium hydroxide monohydrate (0.61 g, 14.53 mmol, 3 equiv.) portion-wise at 0 °C. The reaction mixture was warmed to room temperature. After stirring at room

temperature for 3 hours, the reaction mixture was acidified by HCl (6 N) to pH 3.0. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the organic layer was combined, dried over Na₂SO₄, and concentrated. LC-MS: calculated [M+H]⁺ 352.18, found 352.

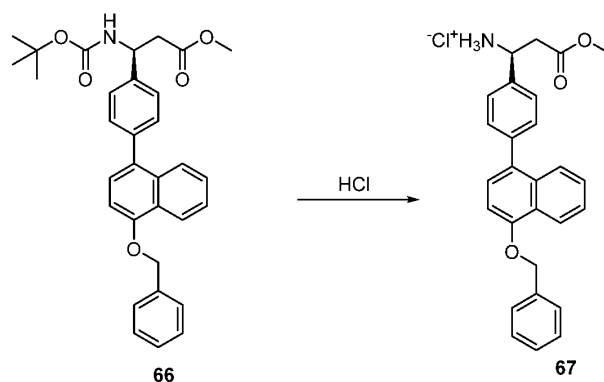


[0308] To a solution of compound 63 (1.88 g, 6.0 mmol, 1.0 equiv.) in anhydrous THF (20 mL) was added n-BuLi in hexane (3.6 mL, 9.0 mmol, 1.5 equiv.) drop-wise at -78 °C. The reaction was kept at -78 °C for another 1 hour. Triisopropylborate (2.08 mL, 9.0 mmol, 1.5 equiv.) was then added into the mixture at -78 °C. The reaction was then warmed up to room temperature and stirred for another 1 hour. The reaction was quenched by saturated NH₄Cl solution (20 mL) and the pH was adjusted to 3. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the organic phase was combined, dried over Na₂SO₄, and concentrated.

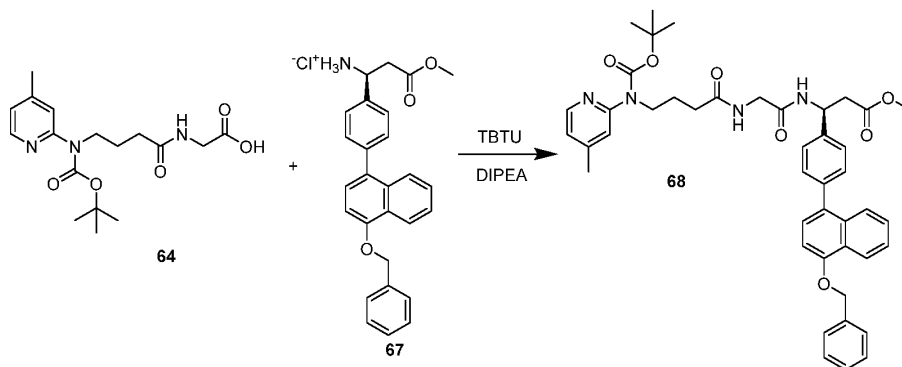


[0309] Compound 12 (300 mg, 0.837 mmol, 1.0 equiv.), Compound 65 (349 mg, 1.256 mmol, 1.5 equiv.), XPhos Pd G2 (13 mg, 0.0167 mmol, 0.02 equiv.), and K₃PO₄ (355 mg, 1.675 mmol, 2.0 equiv.) were mixed in a round-bottom flask. The flask was sealed with a screw-cap septum, and then evacuated and backfilled with nitrogen (this process was repeated a total of 3 times). Then, THF (8 mL) and water (2 mL) were added via syringe. The mixture was bubbled with nitrogen for 20 min and the reaction was kept at room

temperature for overnight. The reaction was quenched with water (10 mL), and the aqueous phase was extracted with ethyl acetate (3×10 mL). The organic phase was dried over Na_2SO_4 , concentrated, and purified via CombiFlash® using silica gel as the stationary phase and was eluted with 15% EtOAc in hexane. LC-MS: calculated $[\text{M}+\text{H}]^+$ 512.24, found 512.56.

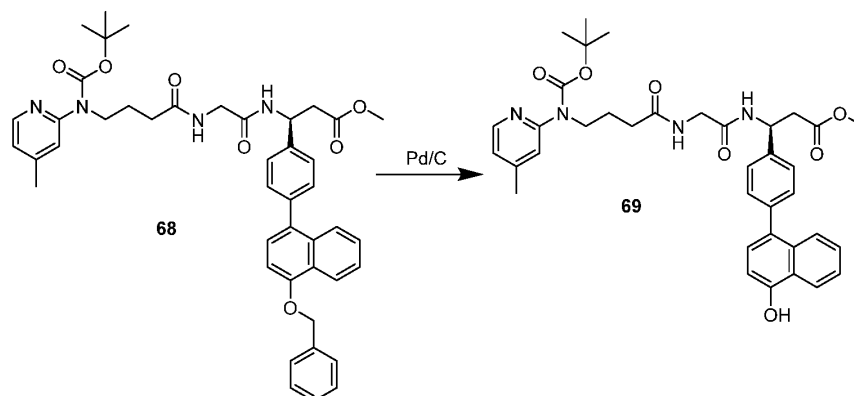


[0310] Compound 66 (858 mg, 1.677 mmol, 1.0 equiv.) was cooled by ice bath. HCl in dioxane (8.4 mL, 33.54 mmol, 20 equiv.) was added into the flask. The reaction was warmed to room temperature and stirred for another 1 hr. The solvent was removed by rotary evaporator and the product was directly used without further purification. LC-MS: calculated $[\text{M}+\text{H}]^+$ 412.18, found 412.46.

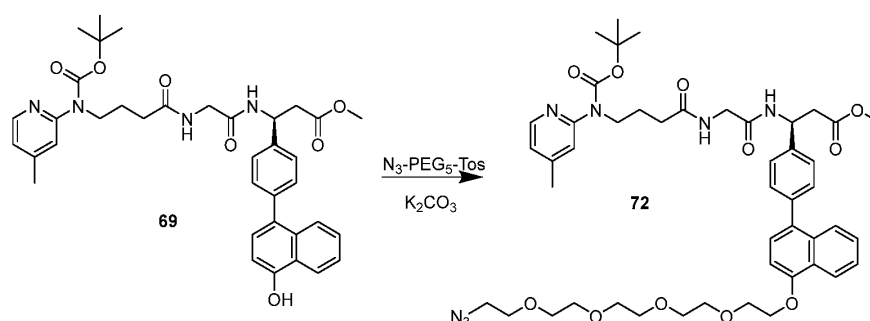


[0311] To a solution of compound 64 (500 mg, 1.423 mmol, 1 equiv.), compound 67 (669 mg, 1.494 mmol, 1.05 equiv.), and TBTU (548 mg, 0.492 mmol, 1.2 equiv.) in anhydrous DMF (15 mL) was added diisopropylethylamine (0.744 mL, 4.268 mmol, 3 equiv.) at 0 °C. The reaction mixture was warmed to room temperature and stirred for another 1 hr. The reaction was quenched by saturated NaHCO_3 aqueous solution (10 mL) and the product was extracted with ethyl acetate (3×20 mL). The organic phase was combined, dried over

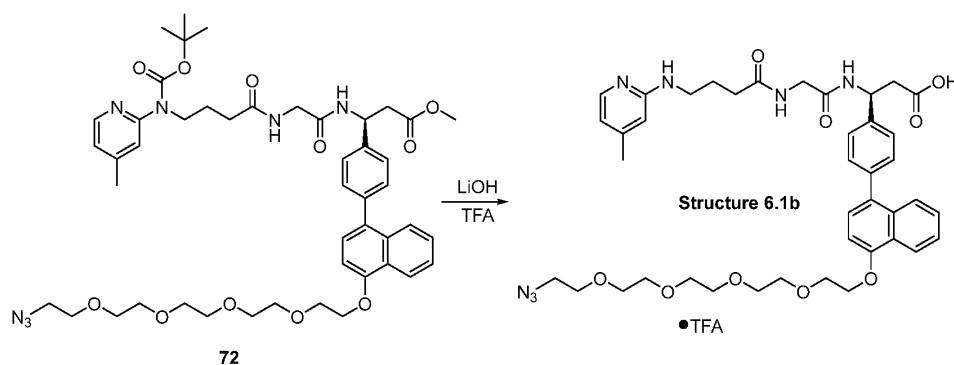
Na₂SO₄, and concentrated. The product was purified by CombiFlash® using silica gel as the stationary phase and was eluted with 3-4% methanol in DCM. The yield was 96.23%. LC-MS: calculated [M+H]⁺ 745.35, found 746.08.



[0312] To a solution of compound 68 (1.02 g, 1.369 mmol, 1 equiv.) in ethyl acetate (10 mL) was added 10% Pd/C (0.15 g, 50% H₂O) at room temperature. The reaction mixture was warmed to room temperature and the reaction was monitored by LC-MS. The reaction was kept at room temperature overnight. The solids were filtered through Celite® and the solvent was removed by rotary evaporator. The product was directly used without further purification. LC-MS: [M+H]⁺ 655.31, found 655.87.



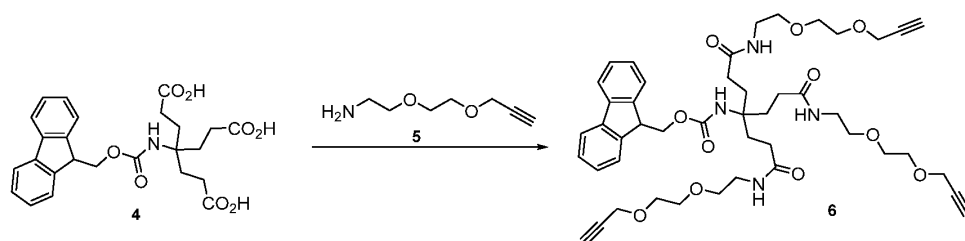
[0313] To a solution of compound 69 (100 mg, 0.152 mmol, 1 equiv.) and azido-PEG₅-OTs (128 mg, 0.305 mmol, 2 equiv.) in anhydrous DMF (2 mL) was added K₂CO₃ (42 mg, 0.305 mmol, 2 equiv.) at 0 °C. The reaction mixture was stirred for 6 hours at 80 °C. The reaction was quenched by saturated NaHCO₃ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic phase was combined, dried over Na₂SO₄, and concentrated. LC-MS: calculated [M+H]⁺ 900.40, found 901.46.



[0314] To a solution of compound 72 (59 mg, 0.0656 mmol, 1.0 equiv.) in THF (2 mL) and water (2 mL) was added lithium hydroxide (5 mg, 0.197 mmol, 3.0 equiv.) at room temperature. The mixture was stirred at room temperature for another 1 hr. The pH was adjusted to 3.0 by HCl (6N) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The organic phase was combined, dried over Na₂SO₄, and concentrated. TFA (0.5 mL) and DCM (0.5 mL) was added into the residue and the mixture was stirred at room temperature for another 3 hr. The solvent was removed by rotary evaporator. LC-MS: calculated [M+H]⁺ 786.37, found 786.95.

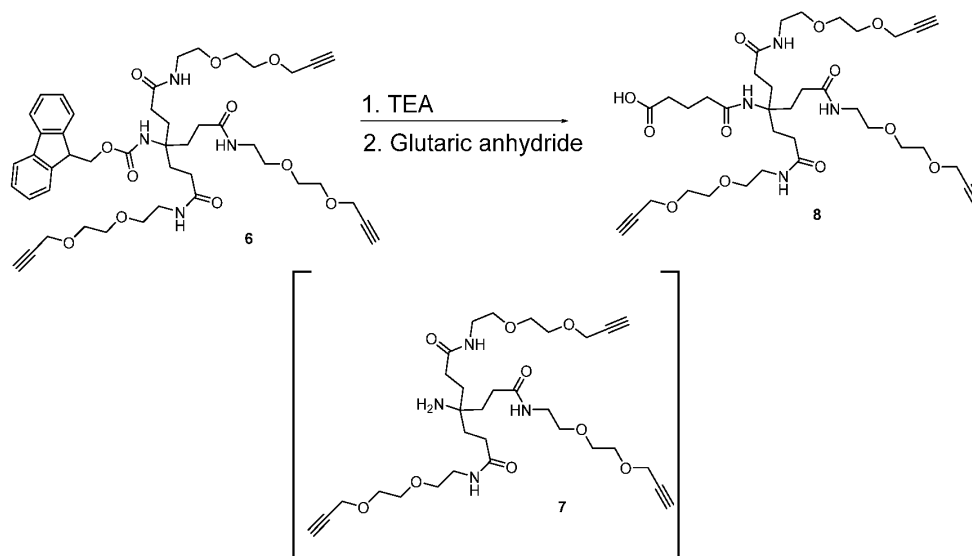
[0315] *G. Synthesis of TriAlk 14*

[0316] TriAlk14 and (TriAlk14)s as shown in Table 12, above, may be synthesized using the synthetic route shown below. Compound 14 may be added to the sense strand as a phosphoramidite using standard oligonucleotide synthesis techniques, or compound 22 may be conjugated to the sense strand comprising an amine in an amide coupling reaction.



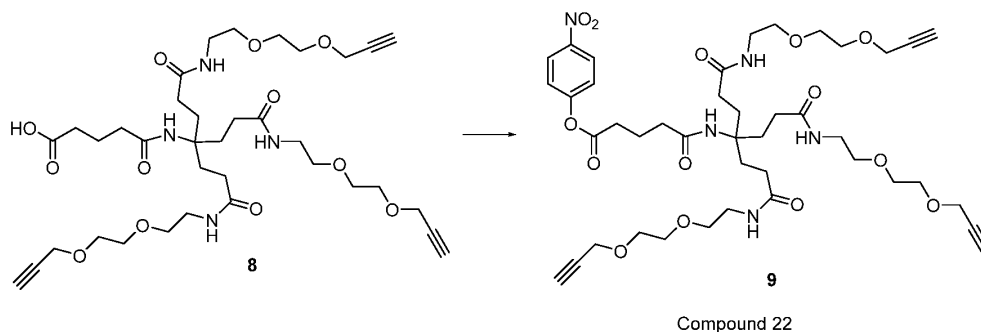
[0317] To a 3-L jacketed reactor was added 500 mL DCM and **4** (75.0 g, 0.16 mol). The internal temperature of the reaction was cooled to 0 °C and TBTU (170.0 g, 0.53 mol) was added. The suspension was then treated with the amine **5** (75.5 g, 0.53 mol) dropwise keeping the internal temperature less than 5 °C. The reaction was then treated with DIPEA (72.3 g, 0.56 mol) slowly, keeping the internal temperature less than 5 °C. After the addition was complete, the reaction was warmed up to 23 °C over 1 hour, and allowed to

stir for 3 hours. A 10% kicker charge of all three reagents were added and allowed to stir an additional 3 hours. The reaction was deemed complete when <1% of **4** remained. The reaction mixture was washed with saturated ammonium chloride solution (2 x 500 mL) and once with saturated sodium bicarbonate solution (500 mL). The organic layer was then dried over sodium sulfate and concentrated to an oil. The mass of the crude oil was 188 g which contained 72% **6** by QNMR. The crude oil was carried to the next step. Calculated mass for $C_{46}H_{60}N_4O_{11}$ = 845.0 m/z. Found $[M+H]^+$ = 846.0.

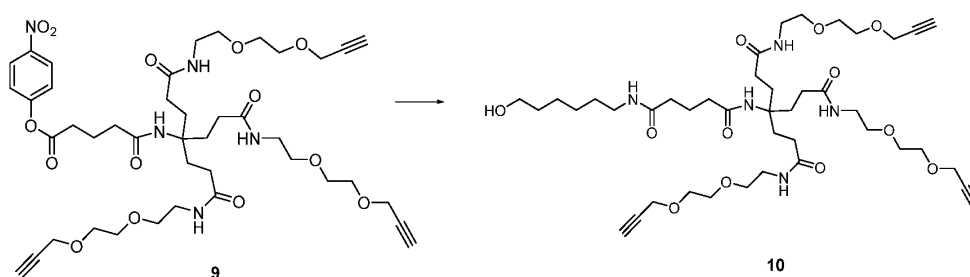


[0318] The 121.2 g of crude oil containing 72 wt% compound **6** (86.0 g, 0.10 mol) was dissolved in DMF (344 mL) and treated with TEA (86 mL, 20 v/v%), keeping the internal temperature below 23 °C. The formation of dibenzofulvene (DBF) relative to the consumption of Fmoc-amine **6** was monitored via HPLC method 1 (Figure 2) and the reaction was complete within 10 hours. To the solution was added glutaric anhydride (12.8 g, 0.11 mol) and the intermediate amine **7** was converted to compound **8** within 2 hours. Upon completion, the DMF and TEA were removed at 30 °C under reduced pressure resulting in 100 g of a crude oil. Due to the high solubility of compound **7** in water, an aqueous workup could not be used, and chromatography is the only way to remove DBF, TMU, and glutaric anhydride. The crude oil (75 g) was purified on a Teledyne ISCO Combi-flash® purification system in three portions. The crude oil (25 g) was loaded onto a 330 g silica column and eluted from 0 – 20% methanol/DCM over 30 minutes resulting

in 42 g of compound **8** (54% yield over 3 steps). Calculated mass for $C_{36}H_{55}N_4O_{12}$ = 736.4 m/z. Found $[M+H] = 737.0$.

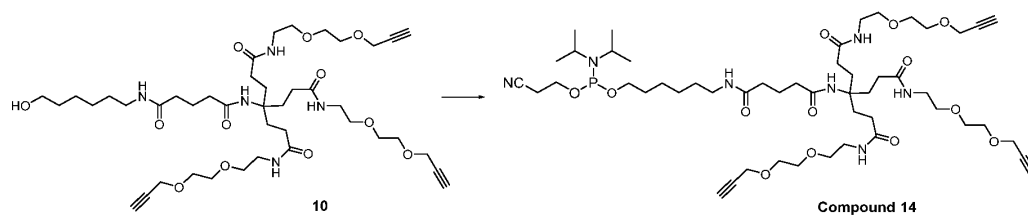


[0319] Compound **8** (42.0 g, 0.057 mol) was co-stripped with 10 volumes of acetonitrile prior to use to remove any residual methanol from chromatography solvents. The oil was redissolved in DMF (210 mL) and cooled to 0 °C. The solution was treated with 4-nitrophenol (8.7 g, 0.063 mol) followed by EDC-hydrochloride (12.0 g, 0.063 mol) and found to reach completion within 10 hours. The solution was cooled to 0 °C and 10 volumes ethyl acetate was added followed by 10 volumes saturated ammonium chloride solution, keeping the internal temperature below 15 °C. The layers were allowed to separate and the ethyl acetate layer was washed with brine. The combined aqueous layers were extracted twice with 5 volumes ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to an oil. The crude oil (55 g) was purified on a Teledyne ISCO Combi-Flash® purification system in three portions. The crude oil (25 g) was loaded onto a 330 g silica column and eluted from 0 – 10% methanol/DCM over 30 minutes resulting in 22 g of pure **9** (**Compound 22**) (50% yield). Calculated mass for $C_{42}H_{59}N_5O_{14}$ = 857.4 m/z. Found $[M+H] = 858.0$.



[0320] A solution of ester **9** (49.0 g, 57.1 mmol) and 6-amino-1-hexanol (7.36 g, 6.28 mmol) in dichloromethane (3 volumes) was treated with triethylamine (11.56g, 111.4 mmol) dropwise. The reaction was monitored by observing the disappearance of

compound **9** on HPLC Method 1 and was found to be complete in 10 minutes. The crude reaction mixture was diluted with 5 volumes dichloromethane and washed with saturated ammonium chloride (5 volumes) and brine (5 volumes). The organic layer was dried over sodium sulfate and concentrated to an oil. The crude oil was purified on a Teledyne ISCO Combi-flash® purification system using a 330 g silica column. The 4-nitrophenol was eluted with 100% ethyl acetate and **10** was flushed from the column using 20% methanol/DCM resulting in a colorless oil (39 g, 81% yield). Calculated mass for $C_{42}H_{69}N_5O_{12}$ = 836.0 m/z. Found $[M+H] = 837.0$.



[0321] Alcohol **10** was co-stripped twice with 10 volumes of acetonitrile to remove any residual methanol from chromatography solvents and once more with dry dichloromethane (KF < 60 ppm) to remove trace water. The alcohol **10** (2.30 g, 2.8 mmol) was dissolved in 5 volumes dry dichloromethane (KF < 50 ppm) and treated with diisopropylammonium tetrazolide (188 mg, 1.1 mmol). The solution was cooled to 0 °C and treated with 2-cyanoethyl N,N,N',N'-tetraisopropylphosphoramidite (1.00 g, 3.3 mmol) dropwise. The solution was removed from ice-bath and stirred at 20 °C. The reaction was found to be complete within 3 – 6 hours. The reaction mixture was cooled to 0 °C and treated with 10 volumes of a 1:1 solution of saturated ammonium bicarbonate/brine and then warmed to ambient over 1 minute and allowed to stir an additional 3 minutes at 20 °C. The biphasic mixture was transferred to a separatory funnel and 10 volumes of dichloromethane was added. The organic layer was separated and washed with 10 volumes of saturated sodium bicarbonate solution to hydrolyze unreacted bis-phosphorous reagent. The organic layer was dried over sodium sulfate and concentrated to an oil resulting in 3.08 g of 94 wt% Compound **14**. Calculated mass for $C_{51}H_{86}N_7O_{13}P$ = 1035.6 m/z. Found $[M+H] = 1036$.

[0322] *H. Conjugation of Targeting Ligands.* Either prior to or after annealing, the 5' or 3' tridentate alkyne functionalized sense strand is conjugated to targeting ligands. The following example describes the conjugation of targeting ligands to the annealed duplex: Stock solutions of 0.5M Tris(3-hydroxypropyltriazolylmethyl)amine (THPTA), 0.5M of Cu(II) sulfate pentahydrate ($Cu(II)SO_4 \cdot 5H_2O$) and 2M solution of sodium ascorbate were

prepared in deionized water. A 75 mg/mL solution in DMSO of targeting ligand was made. In a 1.5 mL centrifuge tube containing tri-alkyne functionalized duplex (3mg, 75 μ L, 40mg/mL in deionized water, ~15,000 g/mol), 25 μ L of 1M Hepes pH 8.5 buffer is added. After vortexing, 35 μ L of DMSO was added and the solution is vortexed. Targeting ligand was added to the reaction (6 equivalents/duplex, 2 equivalents/alkyne, ~15 μ L) and the solution is vortexed. Using pH paper, pH was checked and confirmed to be pH ~8. In a separate 1.5 mL centrifuge tube, 50 μ L of 0.5M THPTA was mixed with 10 μ L of 0.5M Cu(II)SO₄ · 5H₂O, vortexed, and incubated at room temp for 5 min. After 5 min, THPTA/Cu solution (7.2 μ L, 6 equivalents 5:1 THPTA:Cu) was added to the reaction vial, and vortexed. Immediately afterwards, 2M ascorbate (5 μ L, 50 equivalents per duplex, 16.7 per alkyne) was added to the reaction vial and vortexed. Once the reaction was complete (typically complete in 0.5-1h), the reaction was immediately purified by non-denaturing anion exchange chromatography.

Example 2. *In Vitro* Testing of MUC5AC RNAi Agents.

[0323] Certain chemically modified candidate sequence duplexes shown Table 8C above (with the antisense strand sequence set forth in Table 3 and the nucleotide and end cap portion of the sense strand found in Table 6), were tested *in vitro*. The MUC5AC RNAi agents were prepared in accordance with the procedures set forth in Example 1.

[0324] Evaluation of MUC5AC RNAi agents *in vitro* was performed by transfection of A549 cells, a human lung epithelial cell line. Cells were plated at ~7,500 cells per well in 96-well format, and each of the RNAi agent duplexes shown in Table 12 was transfected at three concentrations (10 nM, 1 nM, and 0.1 nM), using LipoFectamine RNAiMax (Thermo Fisher) transfection reagent. Relative expression of each of the MUC5AC RNAi agents was determined by qRT-PCR by comparing the expression levels of MUC5AC mRNA to an endogenous control, and normalized to untreated A549 cells ($\Delta\Delta C_T$ analysis), as shown in Table 12.

[0325] Table 12, below, lists the AD duplex number for the sequence being examined, as well as in parenthesis the gene position being targeted by that particular RNAi agent. Thus, for example, for Duplex ID AD08101, average relative expression at 1 nM of 0.377 shows MUC5AC gene knockdown of 62.3%, and average relative expression at 0.1 nM shows inhibition of 53.0% (0.470) normalized to untreated wells (mock control).

Table 13. In Vitro Testing of MUC5AC RNAi Agents.

Duplex ID No.	Avg. Rel. Exp. 10 nM	High (error)	Low (error)	Avg. Rel. Exp. 1 nM	High (error)	Low (error)	Avg. Rel. Exp. 0.1 nM	High (error)	Low (error)
AD08101 (11014_1)	0.230	0.042	0.051	0.377	0.049	0.056	0.470	0.056	0.064
AD08666 (4993_2)	0.258	0.047	0.058	0.394	0.068	0.082	0.474	0.102	0.131
AD08668 (4993_4)	0.228	0.052	0.068	0.401	0.065	0.078	0.554	0.181	0.270
AD07732 (3099_1)	0.240	0.057	0.075	0.427	0.083	0.103	0.527	0.087	0.105
AD08100 (10206_1)	0.286	0.031	0.035	0.382	0.048	0.054	0.550	0.081	0.096
AD08103 (12965_1)	0.198	0.063	0.092	0.439	0.079	0.097	0.656	0.086	0.099
AD07734 (5347_1)	0.186	0.047	0.062	0.515	0.089	0.107	0.614	0.085	0.099
AD07634 (3535_1)	0.161	0.025	0.030	0.423	0.046	0.051	0.769	0.129	0.154
AD08671 (4992_2)	0.353	0.047	0.054	0.416	0.078	0.096	0.588	0.068	0.077
AD07763 (610_1)	0.138	0.034	0.046	0.432	0.065	0.077	0.826	0.149	0.182
AD08667 (4993_3)	0.293	0.056	0.069	0.427	0.051	0.057	0.677	0.151	0.195
AD07733 (4993_1)	0.253	0.031	0.036	0.501	0.084	0.102	0.655	0.123	0.152
AD08669 (4993_5)	0.302	0.037	0.042	0.461	0.057	0.065	0.658	0.083	0.094
AD08673 (4992_4)	0.369	0.061	0.073	0.468	0.060	0.069	0.624	0.070	0.079
AD07774 (2797_1)	0.182	0.053	0.074	0.565	0.088	0.104	0.860	0.099	0.112

Duplex ID No.	Avg. Rel. Exp. 10 nM	High (error)	Low (error)	Avg. Rel. Exp. 1 nM	High (error)	Low (error)	Avg. Rel. Exp. 0.1 nM	High (error)	Low (error)
AD07735 (5350 1)	0.288	0.037	0.043	0.565	0.097	0.117	0.774	0.071	0.078
AD08670 (4993 6)	0.360	0.033	0.036	0.513	0.072	0.084	0.814	0.198	0.261
AD07637 (5300 1)	0.539	0.061	0.069	0.606	0.057	0.063	0.674	0.051	0.055
AD08571 (15051 1)	0.250	0.039	0.047	0.612	0.046	0.050	0.978	0.089	0.099
AD08572 (15052 7)	0.389	0.052	0.059	0.688	0.080	0.091	0.819	0.098	0.112
AD08568 (3910 1)	0.448	0.069	0.082	0.661	0.080	0.091	0.789	0.082	0.092
AD08569 (5029 9)	0.282	0.034	0.038	0.666	0.096	0.113	0.978	0.046	0.048
AD08573 (15052 8)	0.398	0.027	0.029	0.736	0.069	0.076	0.814	0.118	0.138
AD08096 (4992 1)	0.359	0.040	0.045	0.621	0.076	0.086	1.008	0.080	0.087
AD08672 (4992 3)	0.432	0.052	0.059	0.669	0.057	0.063	0.925	0.040	0.042
AD07756 (1618 1)	0.372	0.064	0.078	0.693	0.053	0.058	1.082	0.146	0.169
AD07773 (2536 1)	0.446	0.042	0.046	0.837	0.117	0.136	0.935	0.153	0.183
AD07760 (2001 1)	0.379	0.059	0.070	0.806	0.141	0.171	1.096	0.151	0.175
AD07771 (2004 1)	0.389	0.032	0.035	0.872	0.093	0.104	1.205	0.161	0.185
Mock Control	1.000	0.164	0.197	1.000	0.164	0.197	1.000	0.164	0.197

Example 3. In Vitro Testing of MUC5AC RNAi Agents.

[0327] Certain chemically modified candidate sequence duplexes shown Table 8C above (with the antisense strand sequence set forth in Table 3 and the nucleotide and end cap portion of the sense strand found in Table 6), were tested *in vitro*. The MUC5AC RNAi agents were prepared in accordance with the procedures set forth in Example 1.

[0328] Evaluation of MUC5AC RNAi agents *in vitro* was performed by transfection of A549 cells, a human lung epithelial cell line. Cells were plated at ~7,500 cells per well in 96-well format, and each of the RNAi agent duplexes shown in Table 12 was transfected at three concentrations (10 nM, 1 nM, and 0.1 nM), using LipoFectamine RNAiMax (Thermo Fisher) transfection reagent. Relative expression of each of the MUC5AC RNAi agents was determined by qRT-PCR by comparing the expression levels of MUC5AC mRNA to an endogenous control, and normalized to untreated A549 cells ($\Delta\Delta C_T$ analysis), as shown in Table 12.

[0329] Table 12, below, lists the AD duplex number for the sequence being examined, as well as in parenthesis the gene position being targeted by that particular RNAi agent. Thus, for example, for Duplex ID AD08101, average relative expression at 1 nM of 0.377 shows MUC5AC gene knockdown of 62.3%, and average relative expression at 0.1 nM shows inhibition of 53.0% (0.470) normalized to untreated wells (mock control).

Table 14. In Vitro Testing of MUC5AC RNAi Agents.

Duplex ID No.	Avg. Rel. Exp. 10 nM	High (error)	Low (error)	Avg. Rel. Exp. 1 nM	High (error)	Low (error)	Avg. Rel. Exp. 0.1 nM	High (error)	Low (error)
AD07733 (4993_1)	0.156	0.047	0.067	0.192	0.030	0.035	0.336	0.024	0.026
AD08096 (4992_1)	0.171	0.022	0.026	0.275	0.035	0.040	0.406	0.027	0.028
AD07767 (1758_1)	0.140	0.019	0.022	0.195	0.097	0.193	0.536	0.226	0.392
AD08103 (12965_1)	0.197	0.057	0.080	0.276	0.042	0.050	0.409	0.046	0.052
AD08098 (8739_1)	0.172	0.032	0.039	0.259	0.076	0.109	0.466	0.042	0.046
AD07763 (610_1)	0.094	0.024	0.032	0.293	0.033	0.037	0.514	0.026	0.027
AD08100 (10206_1)	0.242	0.046	0.056	0.260	0.051	0.064	0.417	0.041	0.045
AD08101 (11014_1)	0.236	0.054	0.071	0.322	0.044	0.052	0.364	0.039	0.043
AD07751 (5533_1)	0.161	0.058	0.091	0.335	0.051	0.061	0.536	0.035	0.037
AD07634 (3535_1)	0.159	0.034	0.043	0.385	0.035	0.039	0.507	0.061	0.069
AD07770 (1867_1)	0.114	0.022	0.028	0.377	0.041	0.046	0.599	0.059	0.066
AD07747 (5020_1)	0.347	0.057	0.069	0.330	0.042	0.049	0.413	0.033	0.036
AD07749 (5441_1)	0.365	0.061	0.073	0.337	0.017	0.018	0.464	0.060	0.068
AD08095 (1871_1)	0.204	0.024	0.027	0.380	0.064	0.077	0.624	0.046	0.049
AD08097 (6798_1)	0.364	0.056	0.066	0.384	0.068	0.083	0.511	0.061	0.069

Duplex ID No.	Avg. Rel. Exp. 10 nM	High (error)	Low (error)	Avg. Rel. Exp. 1 nM	High (error)	Low (error)	Avg. Rel. Exp. 0.1 nM	High (error)	Low (error)
AD07750 (519 1)	0.432	0.063	0.074	0.240	0.073	0.105	0.589	0.056	0.062
AD07774 (297 1)	0.168	0.031	0.038	0.432	0.072	0.087	0.679	0.040	0.042
AD07732 (309 1)	0.352	0.056	0.067	0.402	0.147	0.231	0.535	0.154	0.217
AD07764 (923 1)	0.424	0.080	0.099	0.431	0.051	0.057	0.505	0.048	0.052
AD07771 (2004 1)	0.367	0.064	0.077	0.493	0.090	0.109	0.597	0.078	0.090
AD07748 (5042 1)	0.518	0.131	0.176	0.413	0.078	0.095	0.559	0.068	0.077
AD07768 (1761 1)	0.278	0.039	0.046	0.561	0.084	0.099	0.728	0.041	0.043
AD07756 (1618 1)	0.522	0.081	0.096	0.464	0.081	0.099	0.708	0.052	0.056
AD07772 (2234 1)	0.476	0.055	0.062	0.588	0.057	0.063	0.654	0.070	0.078
AD07773 (2536 1)	0.498	0.039	0.043	0.596	0.060	0.067	0.672	0.055	0.060
AD07746 (4446 1)	0.578	0.058	0.065	0.671	0.086	0.099	0.740	0.052	0.056
AD08094 (1445 1)	0.646	0.056	0.061	0.721	0.071	0.079	0.762	0.076	0.084
AD07766 (1446 1)	0.760	0.103	0.119	0.806	0.067	0.072	0.793	0.082	0.092
AD07745 (4443 1)	0.902	0.194	0.247	0.840	0.088	0.098	0.821	0.049	0.052
Mock Control	1.000	0.109	0.122	1.000	0.109	0.122	1.000	0.109	0.122

Example 4. House Dust Mite (HDM) Induced Allergic Asthma Model.

[0331] To study the properties of certain MUC5AC RNAi agents *in vivo*, the house dust mite (HDM) induced allergic asthma mouse model was used. To induce mouse Muc5ac expression, female Balb/c mice (6-8 weeks in age) were administered 50 µg house dust mite protein acquired commercially in 25 µL of isotonic saline intranasally using a pipette for 5 consecutive days. 72 hours after the fifth daily dose, mice were euthanized and whole lungs were harvested for mRNA expression analysis. Compared to unchallenged, naïve mice, relative expression of mouse Muc5ac mRNA in HDM challenged mice is shown to increase approximately 100 fold.

10

Example 5. In Vivo Intratracheal Administration of MUC5AC RNAi Agents in the HDM Model.

[0332] The HDM induced allergic asthma mouse model described in Example 4, above, was used. The following Table 15 sets forth the dosing Groups:

15

[0333] **Table 15.** MUC5AC RNAi Agent and Dosing for Example 5.

GROUP	IT Dose Administered	Study Days IT Administered	IN Dose Administered	Study Days IN Dose Administered	Animals Per Group
1	No treatment	N/A	No treatment	N/A	6
2	No treatment	N/A	Saline	Days 8-12	6
3	Saline	1, 3, 5, and 8	Saline	Days 8-12	3
4	No treatment	N/A	HDM	Days 8-12	6
5	Saline	1, 3, 5, and 8	HDM	Days 8-12	4
6	5.0 mg/kg Tri-SM6, 1- α v β 6-AD07022	1, 3, 5, and 8	HDM	Days 8-12	4
7	5.0 mg/kg Tri-SM6, 1- α v β 6-AD07720	1, 3, 5, and 8	HDM	Days 8-12	5
8	5.0 mg/kg Tri-SM6, 1- α v β 6-AD07719	1, 3, 5, and 8	HDM	Days 8-12	5

[0334] As noted in Table 15 above, the mice in Group 1 received no treatment throughout. For the mice in Groups 3, 5, 6, 7 and 8, on study days 1, 3, 5, and 8, female Balb/c mice were administered a single dose of 50 microliters via a microsprayer device (Penn Century, Philadelphia, PA) suitable for intratracheal (IT) administration of isotonic saline or 5.0 mg/kg the respective MUC5AC RNAi agent formulated in isotonic saline as noted in Table 15.

[0335] As shown in Table 15, each of the MUC5AC RNAi agents (Groups 6, 7 and 8) were conjugated to a tridentate small molecule $\alpha\beta 6$ epithelial cell targeting ligand (Tri-SM6.1, *see Fig. 1*) at the 5' terminal end of the sense strand.

[0336] The chemically modified sequences for MUC5AC RNAi agents AD07720 and AD07719 (Groups 7 and 8) are shown in Table 7B (showing duplex), Table 3 (showing respective antisense strand), and Table 5 (showing respective sense strand with linker but without tridentate small molecule $\alpha\beta 6$ epithelial cell targeting ligand (Tri-SM6.1).

[0337] AD07022 has mouse-specific sequences that do not have homology with the human MUC5AC gene, and were chemically modified as follows:

Tri-SM6.1- $\alpha\beta 6$ -AD07022

Modified Sense Strand (5' → 3'):

20 Tri-SM6.1- $\alpha\beta 6$ -(TA14)cscauacagCfAfGfuacaguacac(invAb) (SEQ ID NO:1714)

Modified Antisense Strand (5' → 3'):

cPrpusGfsusAfaCfuGfuAfcUfgCfuGfuAfuGfsg (SEQ ID NO:1713)

[0338] On each of Days 8 through 12, the mice in Groups 2 through 8 were administered a single dose intranasally (IN) using a pipette with 25 microliters of isotonic saline (Groups 2 and 3) or 50 micrograms of house dust mite formulated in isotonic saline (referred to in Table 15 as HDM).

[0339] Mice were sacrificed on study day 15, and total RNA was isolated from both lungs following collection and homogenization. Mouse Muc5ac mRNA expression was quantitated by probe-based quantitative PCR, normalized to mouse beta-actin expression, and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

[0340] **Table 16.** Average Relative Mouse MUC5AC mRNA at Sacrifice (Day 15) in Example 5

Group ID	Average Relative mMuc5AC mRNA	Low (error)	High (error)
Group 1 (No Treatment)	1.000	0.213	0.270
Group 2 (IN Saline)	1.941	0.638	0.951
Group 3 (IT Saline & IN Saline)	1.706	0.532	0.774
Group 4 (IN HDM)	117.876	26.269	33.801
Group 5 (IT Saline & IN HDM)	95.585	21.822	28.277
Group 6 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta\text{6}$ -AD07022 & IN HDM)	13.444	3.410	4.569
Group 7 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta\text{6}$ -AD07720 & IN HDM)	71.812	16.633	21.647
Group 8 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta\text{6}$ -AD07719 & IN HDM)	90.537	27.214	38.910

The data were normalized to the non-treatment group (Group 1). As shown in the data in Table 16 above, the HDM mouse model performed as expected with respect to promoting an increase in MUC5AC expression after exposure to HDM. The data show that Groups 7 and 8, which each had nucleotide sequences targeting position 1921 of the MUC5AC gene and has homology to both the human and mouse gene transcript, provided only a very minimal reduction in MUC5AC protein compared to the HDM model mice of Groups 4 and 5 with no RNAi agent, indicating only a minimal amount of inhibition for these specific RNAi agents. Alternatively, the mouse-specific RNAi agent of AD07022 (Group 6) showed a substantial reduction in Muc5ac mouse mRNA levels (only 13.444) compared to the groups where HDM was administered without a MUC5AC RNAi agent.

15 **Example 6. In Vivo Intratracheal Administration of MUC5AC RNAi Agents in the HDM Model.**

[0341] The HDM induced allergic asthma mouse model described in Example 4, above, was used. The following Table 17 sets forth the dosing Groups:

[0342] Table 17. MUC5AC RNAi Agent and Dosing for Example 6.

GROUP	IT Dose Administered	Study Days IT Administered	IN Dose Administered	Study Days IN Dose Administered	Animals Per Group	Targeted Gene Position
1	Saline	1, 3, 5, and 8	Saline	Days 8-12	6	N/A
2	Saline	1, 3, 5, and 8	HDM	Days 8-12	5	N/A
3	5.0 mg/kg Tri-SM6.1- α v β 6-AD07022	1, 3, 5, and 8	HDM	Days 8-12	6	Mouse-specific
4	5.0 mg/kg Tri-SM6.1- α v β 6-AD08083	1, 3, 5, and 8	HDM	Days 8-12	5	5029
5	5.0 mg/kg Tri-SM6.1- α v β 6-AD08084	1, 3, 5, and 8	HDM	Days 8-12	5	5029
6	5.0 mg/kg Tri-SM6.1- α v β 6-AD08085	1, 3, 5, and 8	HDM	Days 8-12	4	5029
7	5.0 mg/kg Tri-SM6.1- α v β 6-AD08086	1, 3, 5, and 8	HDM	Days 8-12	5	9729
8	5.0 mg/kg Tri-SM6.1- α v β 6-AD08087	1, 3, 5, and 8	HDM	Days 8-12	6	9729
9	5.0 mg/kg Tri-SM6.1- α v β 6-AD08088	1, 3, 5, and 8	HDM	Days 8-12	5	15052
10	5.0 mg/kg Tri-SM6.1- α v β 6-AD08089	1, 3, 5, and 8	HDM	Days 8-12	5	15052
11	5.0 mg/kg Tri-SM6.1- α v β 6-AD07022	1 and 8	HDM	Days 8-12	5	Mouse-specific

[0343] For the mice in Groups 1-10, on study days 1, 3, 5, and 8, female Balb/c mice were administered a single dose of 50 microliters via a microsyringe device (Penn Century, Philadelphia, PA) suitable for intratracheal (IT) administration of isotonic saline or 5.0 mg/kg of the respective MUC5AC RNAi agent formulated in isotonic saline as noted in Table 17. For the mice in Group 11, the MUC5AC RNAi agent was administered only on days 1 and 8.

[0344] As shown in Table 17, each of the MUC5AC RNAi agents (Groups 3-11) were conjugated to a tridentate small molecule $\alpha\beta 6$ epithelial cell targeting ligand (Tri-SM6.1, *see* Fig. 1) at the 5' terminal end of the sense strand. The chemically modified sequences for MUC5AC RNAi agents AD08083, AD08084, AD08085, AD08086, AD08087, AD08088, and AD08089 (Groups 4 through 10) are shown in Table 7B (showing duplex), Table 3 (showing respective antisense strand), and Table 5 (showing respective sense strand with linker but without tridentate small molecule $\alpha\beta 6$ epithelial cell targeting ligand (Tri-SM6.1)).

[0345] AD07022 has mouse-specific sequences that do not have homology with the human MUC5AC gene, and were chemically modified as shown above in Example 5.

[0346] On each of Days 8 through 12, the mice were administered a single dose intranasally (IN) using a pipette with 25 microliters of isotonic saline (Group 2) or 50 micrograms of house dust mite formulated in isotonic saline (referred to in Table 17 as HDM).

[0347] Mice were sacrificed on study day 15, and total RNA was isolated from both lungs following collection and homogenization. Mouse Muc5ac mRNA expression was quantitated by probe-based quantitative PCR, normalized to mouse beta-actin expression, and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

[0348] **Table 18.** Average Relative Mouse MUC5AC mRNA at Sacrifice (Day 15) in Example 6

Group ID	Average Relative mMuc5ac mRNA	Low (error)	High (error)
Group 1 (IT Saline & IN Saline)	1.000	0.305	0.440
Group 2 (IT Saline & IN HDM)	115.127	17.128	20.122

Group 3 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD07022 & IN HDM)	19.053	6.287	9.383
Group 4 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08083 & IN HDM)	35.333	13.193	21.054
Group 5 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08084 & IN HDM)	26.634	12.943	25.180
Group 6 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08085 & IN HDM)	34.602	3.503	3.897
Group 7 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08086 & IN HDM)	55.475	15.377	21.273
Group 8 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08087 & IN HDM)	66.631	19.703	27.976
Group 9 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08088 & IN HDM)	26.879	4.505	5.412
Group 10 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08089 & IN HDM)	14.903	2.441	2.919
Group 11 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD07022 & IN HDM)	14.457	6.005	10.271

[0349] The data were normalized to the IT and IN saline-only dosed group (Group 1). As shown in the data in Table 18 above, the HDM mouse model performed as expected with respect to promoting an increase in MUC5AC expression after exposure to HDM. The data show that Groups 7 and 8, which both had nucleotide sequences targeting position 9729 of the MUC5AC gene and has homology to both the human and mouse gene transcript, provided only a moderate reduction in MUC5AC protein compared to the HDM model mice of Group 2 with no RNAi agent, indicating only a moderate amount of inhibition for these specific RNAi agents. Alternatively, the remaining MUC5AC RNAi agents tested (targeting gene position 5029 in Groups 4-6 and gene position 15052 in Groups 9 and 10) each showed substantial inhibition compared to Group 2, as did the mouse-specific MUC5AC RNAi agent of AD07022 (Group 6).

Example 7. In Vivo Intratracheal Administration of MUC5AC RNAi Agents in Rats.

[0350] The HDM induced allergic asthma mouse model described in Example 4, above, was used. The following Table 19 sets forth certain dosing Groups included in the study:

[0351] Table 19. MUC5AC RNAi Agent and Dosing for Example 7.

GROUP	IT Dose Administered	Study Days IT Administered	IN Dose Administered	Study Days IN Dose Administered	Animals Per Group	Targeted Gene Position
1	Saline	1, 3, 5, and 8	Saline	Days 8-12	6	N/A
2	Saline	1, 3, 5, and 8	HDM	Days 8-12	6	N/A
3	5.0 mg/kg Tri-SM6, 1- α v β 6-AD07022	1, 3, 5, and 8	HDM	Days 8-12	5	Mouse-Specific
4	5.0 mg/kg Tri-SM6, 1- α v β 6-AD08173	1, 3, 5, and 8	HDM	Days 8-12	6	3535
5	5.0 mg/kg Tri-SM6, 1- α v β 6-AD08174	1, 3, 5, and 8	HDM	Days 8-12	6	3535
6	5.0 mg/kg Tri-SM6, 1-avb6-AD08243	1, 3, 5, and 8	HDM	Days 8-12	6	3535
7	5.0 mg/kg Tri-SM6, 1-avb6-AD08244	1, 3, 5, and 8	HDM	Days 8-12	6	3535
8	5.0 mg/kg Tri-SM6, 1-avb6-AD08175	1, 3, 5, and 8	HDM	Days 8-12	6	3535
9	5.0 mg/kg Tri-SM6, 1-avb6-AD08176	1, 3, 5, and 8	HDM	Days 8-12	6	3535
10	5.0 mg/kg Tri-SM6, 1-avb6-AD08177	1, 3, 5, and 8	HDM	Days 8-12	6	3535

[0352] For the mice in Groups 1-5, on study days 1, 3, 5, and 8, female Balb/c mice were administered a single dose of 50 microliters via a microsyringe device (Penn Century, Philadelphia, PA) suitable for intratracheal (IT) administration of isotonic saline or 5.0 mg/kg the respective MUC5AC RNAi agent formulated in isotonic saline as noted in Table 19.

[0353] As shown in Table 19, each of the MUC5AC RNAi agents (Groups 3-5) were conjugated to a tridentate small molecule $\alpha\beta 6$ epithelial cell targeting ligand (Tri-SM6.1, see Fig. 1) at the 5' terminal end of the sense strand. The chemically modified sequences for MUC5AC RNAi agents AD08173 and AD08174 (Groups 4 and 5) are shown in Table 7B (showing duplex), Table 3 (showing respective antisense strand), and Table 5 (showing respective sense strand with linker but without tridentate small molecule $\alpha\beta 6$ epithelial cell targeting ligand (Tri-SM6.1)). Each of the MUC5AC RNAi agents with sequences targeting position 3535 have a mismatch in what is understood to be an important location from the mouse gene, and therefore it is expected that the MUC5AC RNAi agents would show little to no inhibitory activity in view of the mismatch.

[0354] AD07022 has mouse-specific sequences that do not have homology with the human MUC5AC gene, and were chemically modified as shown above in Example 5.

[0355] On each of Days 8 through 12, the mice were administered a single dose intranasally (IN) using a pipette with 25 microliters of isotonic saline (Group 1 only) or 50 micrograms of house dust mite formulated in isotonic saline (referred to in Table 19 as HDM).

[0356] Mice were sacrificed on study day 15, and total RNA was isolated from both lungs following collection and homogenization. Mouse Muc5ac mRNA expression was quantitated by probe-based quantitative PCR, normalized to mouse beta-actin expression, and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

[0357] **Table 20.** Average Relative Mouse MUC5AC mRNA at Sacrifice (Day 15) in Example 7

Group ID	Average Relative mMuc5ac mRNA	Low (error)	High (error)
Group 1 (IT Saline & IN Saline)	1.000	0.197	0.245

Group 2 (IT Saline & IN HDM)	132.247	31.248	40.917
Group 3 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD07022 & IN HDM)	13.139	2.426	2.975
Group 4 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08173 & IN HDM)	96.522	13.056	15.098
Group 5 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08174 & IN HDM)	57.983	15.132	20.476
Group 6 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08243 & IN HDM)	55.592	8.761	10.400
Group 7 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08244 & IN HDM)	75.149	17.661	23.087
Group 8 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08175 & IN HDM)	75.420	10.876	12.708
Group 9 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08176 & IN HDM)	72.203	12.062	14.482
Group 10 (IT 5 mg/kg Tri-SM6.1- $\alpha\text{v}\beta 6$ -AD08177 & IN HDM)	67.222	12.063	14.701

[0358] The data were normalized to the IT and IN saline-only dosed group (Group 1). As noted above, given the nature of the mismatch to the mouse gene for the MUC5AC RNAi agents in Groups 4 and 5 (targeting position 3535 of the human gene), minimal inhibition is expected. As shown in the data in Table 20 above, the HDM mouse model performed as expected with respect to promoting an increase in MUC5AC expression after exposure to HDM, as shown in Groups 1 and 2. Unexpectedly, the MUC5AC RNAi agents targeting position 3535 still showed moderate levels of inhibition despite the mismatch to the mouse gene, indicating that MUC5AC RNAi agents targeting this position may be viable as human therapeutic candidates.

Example 8. In Vivo Intratracheal Administration of MUC5AC RNAi Agents in the HDM Model.

[0359] The HDM induced allergic asthma mouse model described in Example 4, above, was used. The following Table 17 sets forth the dosing Groups:

[0360] Table 21. MUC5AC RNAi Agent and Dosing for Example 8.

GROUP	IT Dose Administered	Study Days IT Administered	IN Dose Administered	Study Days IN Dose Administered	Animals Per Group	Targeted Gene Position
1	Saline	1 and 7	Saline	Days 7-11	6	N/A
2	Saline	1 and 7	HDM	Days 7-11	6	N/A
3	5.0 mg/kg Tri-SM6.1- α v β 6-AD07022	1, 2, 4 and 7	HDM	Days 7-11	6	Mouse-specific
4	5.0 mg/kg Tri-SM6.1- α v β 6-AD07022	1 and 7	HDM	Days 7-11	6	Mouse-specific
5	2.5 mg/kg Tri-SM6.1- α v β 6-AD07022	1 and 7	HDM	Days 7-11	6	Mouse-specific
6	1.0 mg/kg Tri-SM6.1- α v β 6-AD07022	1 and 7	HDM	Days 7-11	6	Mouse-specific
7	5.0 mg/kg Tri-SM6.1- α v β 6-AD08089	1, 2, 4 and 7	HDM	Days 7-11	6	15052
8	5.0 mg/kg Tri-SM6.1- α v β 6-AD08089	1 and 7	HDM	Days 7-11	6	15052
9	2.5 mg/kg Tri-SM6.1- α v β 6-AD08089	1 and 7	HDM	Days 7-11	6	15052
10	1.0 mg/kg Tri-SM6.1- α v β 6-AD08089	1 and 7	HDM	Days 7-11	6	15052
11	1.0 mg/kg Tri-SM6.1- α v β 6-AD08089	1	HDM	Days 7-11	6	15052

[0361] Female Balb/c mice were administered a single dose of 50 microliters via a microsprayer device (Penn Century, Philadelphia, PA) suitable for intratracheal (IT) administration of isotonic saline or an MUC5AC RNAi agent formulated in isotonic saline, on the dates and at the concentrations set forth in Table 21 above.

[0362] As shown in Table 21, each of the MUC5AC RNAi agents (Groups 3-11) were conjugated to a tridentate small molecule $\alpha\beta6$ epithelial cell targeting ligand (*see* Fig. 1) at the 5' terminal end of the sense strand. The chemically modified sequences for MUC5AC RNAi agents AD08089 is shown in Table 7B (showing duplex), Table 3 (showing respective antisense strand), and Table 5 (showing respective sense strand with linker but without tridentate small molecule $\alpha\beta6$ epithelial cell targeting ligand).

[0363] AD07022 has mouse-specific sequences that do not have homology with the human MUC5AC gene, and were chemically modified as shown above in Example 5.

[0364] On each of Days 7 through 11, the mice were administered a single dose intranasally (IN) using a pipette with 25 microliters of isotonic saline (Group 1) or 50 micrograms of house dust mite formulated in isotonic saline (referred to in Table 21 as HDM).

[0365] Mice were sacrificed on study day 14, and total RNA was isolated from both lungs following collection and homogenization. Mouse *Muc5ac* mRNA expression was quantitated by probe-based quantitative PCR, normalized to mouse beta-actin expression, and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

[0366] **Table 22.** Average Relative Mouse MUC5AC mRNA at Sacrifice (Day 14) in Example 8

Group ID	Average Relative mMuc5ac mRNA	Low (error)	High (error)
Group 1 (IT Saline & IN Saline)	1.000	0.315	0.459
Group 2 (IT Saline & IN HDM)	112.848	44.187	72.623
Group 3 (IT 5.0 mg/kg Tri-SM6.1- $\alpha\beta6$ -AD07022 (days 1, 2, 4, & 7) & IN HDM)	12.455	3.896	5.669
Group 4 (IT 5.0 mg/kg Tri-SM6.1- $\alpha\beta6$ -AD07022 (days 1 & 7) & IN HDM)	16.521	4.908	6.982
Group 5 (IT 2.5 mg/kg Tri-SM6.1- $\alpha\beta6$ -AD07022 & IN HDM)	26.846	5.096	6.290

Group 6 (IT 1.0 mg/kg Tri-SM6.1- $\alpha\beta$ 6-AD07022 & IN HDM)	26.521	9.295	14.311
Group 7 (IT 5.0 mg/kg Tri-SM6.1- $\alpha\beta$ 6-AD08089 (days 1, 2, 4, & 7) & IN HDM)	10.978	3.101	4.322
Group 8 (IT 5.0 mg/kg Tri-SM6.1- $\alpha\beta$ 6-AD08089 (days 1 & 7) & IN HDM)	17.629	6.752	10.944
Group 9 (IT 2.5 mg/kg Tri-SM6.1- $\alpha\beta$ 6-AD08089 & IN HDM)	17.746	4.647	6.296
Group 10 (IT 1.0 mg/kg Tri-SM6.1- $\alpha\beta$ 6-AD08089 & IN HDM)	21.106	4.109	5.103
Group 11 (IT 1.0 mg/kg Tri-SM6.1- $\alpha\beta$ 6-AD08089 (day 1 only) & IN HDM)	42.413	14.428	21.868

[0367] The data were normalized to the IT and IN saline-only dosed group (Group 1). As shown in the data in Table 22 above, the HDM mouse model performed as expected with respect to promoting an increase in MUC5AC expression after exposure to HDM. The data show that AD08089, which has nucleotide sequences targeting position 15052 of the MUC5AC gene and has homology to both the human and mouse gene transcript, provided substantial inhibition of MUC5AC and was generally comparable to the highly active mouse-specific MUC5AC RNAi agent of AD07022.

10 **Example 9. In Vivo Inhaled Aerosolized Administration of MUC5AC RNAi Agents in Cynomolgus Monkeys.**

[0368] On study day 1, male cynomolgus monkeys were administered a single dose on each of days 1, 8, and 15 at 1 mg/kg pulmonary deposited dose (PDD) of the MUC5AC RNAi agent AC001305 or AC001306. Using a vibrating mesh nebulizer (Aeroneb Solo), aerosol was delivered to restrained, anesthetized monkeys intubated intratracheally. Intubated animals were connected to a ventilator, which was used to control respiratory minute volume. Test article aerosol was generated via an Aeroneb Solo mesh nebulizer connected in-line with the exposure system. Exposures times were determined from aerosol trials in which the efficiency of the system was determined by placing a filter at the end of the endotracheal tube, collecting the aerosol during the course of the exposure. The MUC5AC RNAi agent was conjugated to a tridentate small molecule $\alpha\beta$ 6 epithelial cell targeting ligand (see Fig. 1) at the 5' terminal end of the sense strand, formulated in isotonic saline. The chemically modified sequences for MUC5AC RNAi agents AC001305 and AC001306 are shown in Table 11. The antisense strand sequence of AC001305 is also shown as

AM12165 in Table 3, and the antisense strand sequence of AC001306 is also shown as AM12166 in Table 3, both of which target position 4993 of the MUC5AC gene.

[0369] The dosing groups were as described in the following Table 23:

5 [0370] **Table 23.** MUC5AC RNAi Agent and Dosing for Example 9

Group ID
Group 1 (isotonic saline on Days 1, 8, 15)
Group 2 (1.0 mg/kg pulmonary deposited dose AC001305 on Days 1, 8, 15)
Group 3 (1.0 mg/kg pulmonary deposited dose AC001306 on Days 1, 8, 15)

[0371] Two (2) monkeys were dosed per group. Monkeys were sacrificed on study day 22, and total RNA was isolated from lung samples following collection and homogenization. The data in Table 24, below, shows mRNA expression sampled from the distal left caudal lobe. Cynomolgus monkey MUC5AC mRNA expression was quantitated by probe-based quantitative PCR, normalized to Cynomolgus monkey beta-actin expression, and expressed as fraction of vehicle control group (geometric mean, +/- 95% confidence interval).

10

15 [0372] **Table 24A.** Cynomolgus Monkey Mucosal Tissue Muc5ac mRNA Relative Expression at Sacrifice in Example 9

Group ID	Relative cMuc5ac mRNA Expression (n=2)	Low (error)	High (error)
Group 1 (isotonic saline)	1.000	0.386	0.628
Group 2 (1.0 mg/kg deposited dose AC001305 on Days 1, 8, 15)	0.034	0.010	0.015
Group 3 (1.0 mg/kg deposited dose AC001306 on Days 1, 8, 15)	0.171	0.085	0.169

[0373] **Table 24B.** Cynomolgus Monkey Right Cranial Hilar Muc5ac mRNA Relative Expression at Sacrifice in Example 9

Group ID	Relative cMuc5ac mRNA Expression	Low (error)	High (error)

	(n=2)		
Group 1 (isotonic saline)	1.000	0.708	2.421
Group 2 (1.0 mg/kg deposited dose AC001305 on Days 1, 8, 15)	0.034	0.010	0.015
Group 3 (1.0 mg/kg deposited dose AC001306 on Days 1, 8, 15)	0.180	0.089	0.174

[0374] **Table 24C.** Cynomolgus Monkey Right Cranial Mid Airway Muc5ac mRNA Relative Expression at Sacrifice in Example 9

Group ID	Relative cMuc5ac mRNA Expression (n=2)	Low (error)	High (error)
Group 1 (isotonic saline)	1.000	0.489	0.956
Group 2 (1.0 mg/kg deposited dose AC001305 on Days 1, 8, 15)	0.162	0.099	0.256
Group 3 (1.0 mg/kg deposited dose AC001306 on Days 1, 8, 15)	0.077	0.041	0.086

- 5 As reported in Tables 24A, 24B, and 24C above, the MUC5AC RNAi agents

Example 10. Aerosolized Administration of MUC5AC RNAi Agents in Sheep.

- [0375] Sheep exposed to inhaled ascaris antigen exhibit responses typical of allergic asthma, including an acute phase response (AR), late phase response (LR), and airway hyperreactivity (AHR) as shown by Abraham et.al. (Am Rev Respir Dis. ,1983), and the model has been shown to respond well to standard of care therapies (Caniga, et.al., J Inflamm., 2013). Accordingly, the model may be used to determine the impact of sheep Muc5ac (sMuc5ac) mRNA silencing on airway mechanics and AHR upon treatment with MUC5AC RNAi agents. Test article delivery to intubated sheep, airway mechanics assessments detecting changes in pulmonary resistance (R_L) following challenge with *Ascaris suum* antigen, and AHR assessments by performing cumulative concentration response curves to inhaled carbachol were performed according to published procedures (Abraham et.al., J Clin Invest., 1994).

[0376] Two (2) ascaris-sensitive sheep with previously established responses to *Ascaris suum* challenge were administered 1 mg/kg pulmonary deposited dose levels of AC000480 on days 1, 8 and 15. The chemical structure of AC000480 is shown, for example, in Table 11 and is designed to target position 3535 on the MUC5AC gene. On day 21, AHR was assessed by determining the cumulative carbachol concentration (in breath units, BU) that increased R_L to 400% over the post-1x PBS value (PC₄₀₀). On day 22, sheep were challenged with *Ascaris suum* extract, and R_L was monitored out to 8 hours post-challenge. On day 23, AHR was again assessed in the same manner as on day 21. To monitor duration of effect, sheep were again challenged with *Ascaris suum* extract on day 51, bracketed on day 50 and day 52 with assessments of AHR.

[0377] Table 25. Airway Mechanics Results

Timepoint	Control Trial (no treatment)				Drug Trial: Day 22				Drug Trial: Day 51			
	Animal #		Animal #		Animal #		Animal #		Animal #		Animal #	
	2489	2497	Mean	S.D.	2489	2497	Mean	S.D.	2489	2497	Mean	S.D.
Baseline	RL	0.99	0.99	0.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00
Post-Ascaris	RL	6.66	6.62	6.64	0.03	4.28	5.21	4.75	0.66	6.35	6.38	0.02
	%	573%	569%	571%	3%	328%	421%	375%	66%	535%	538%	2%
1h	RL	4.51	4.40	4.46	0.08	2.35	3.59	2.97	0.88	4.60	4.61	0.01
	%	356%	344%	350%	8%	135%	259%	197%	88%	360%	361%	1%
2h	RL	2.53	2.57	2.55	0.03	1.81	1.66	1.74	0.11	2.42	2.64	0.16
	%	156%	160%	158%	3%	81%	66%	74%	11%	142%	164%	16%
3h	RL	1.55	1.53	1.54	0.01	1.37	1.36	1.37	0.01	1.68	1.62	0.04
	%	57%	55%	56%	1%	37%	36%	37%	1%	68%	62%	4%
4h	RL	1.06	1.21	1.14	0.11	1.05	1.09	1.07	0.03	1.05	1.07	0.01
	%	7%	22%	15%	11%	5%	9%	7%	3%	5%	7%	1%
5h	RL	1.52	1.66	1.59	0.10	1.14	1.19	1.17	0.04	1.64	1.55	0.06
	%	54%	68%	61%	10%	14%	19%	17%	4%	64%	55%	6%
6h	RL	2.13	2.09	2.11	0.03	1.28	1.34	1.31	0.04	2.07	2.18	0.08
	%	115%	111%	113%	3%	28%	34%	31%	4%	107%	118%	8%
6.5h	RL	2.26	2.21	2.24	0.04	1.51	1.49	1.50	0.01	2.22	2.26	0.03
	%	128%	123%	126%	4%	51%	49%	50%	1%	122%	126%	3%
7h	RL	2.32	2.26	2.29	0.04	1.39	1.40	1.40	0.01	2.37	2.29	0.06
	%	134%	128%	131%	4%	39%	40%	40%	1%	137%	129%	6%
7.5h	RL	2.12	2.16	2.14	0.03	1.27	1.35	1.31	0.06	2.32	2.05	0.19
	%	114%	118%	116%	3%	27%	35%	31%	6%	132%	105%	19%
8h	RL	2.08	2.03	2.06	0.04	1.16	1.28	1.22	0.08	2.12	2.13	0.01
	%	110%	105%	108%	4%	16%	28%	22%	8%	112%	113%	1%

[0378] Table 26: AHR Results

Sheep #	BU Carbachol to Produce PC ₄₀₀	
	Control Trial	
	24h pre-ascaris	24h post Ascaris
2489	24	13
2497	31	13
	Drug Trial: Day 22	
	24h pre-ascaris	24h post Ascaris
2489	25	26
2497	26	25
	Drug Trial: Day 51	
	24h pre-ascaris	24h post Ascaris
2489	26	13
2497	29	12

[0379] As shown in Table 25, treatment with AC000480 resulted in attenuation of AR as well as LR upon challenge on day 22. For example, untreated sheep display a mean LR increase of 126% in R_L at 6.5h compared to baseline, where AC000480 treated sheep on day 22 challenge show a more attenuated LR increase of 50% in R_L at 6.5h compared to baseline. In addition, 24h after the day 22 ascaris challenge both AC000480 treated sheep showed no signs of ascaris induced airway hyperresponsiveness, as shown by equivalent number of carbachol breath units required to produce PC₄₀₀. In contrast, in the control trial without AC000480 treatment, sheep required approximately half the amount of carbachol breath units to induce PC₄₀₀ post-ascaris challenge, signifying airway hyperresponsiveness.

[0380] With no additional dosing after day 15, sheep returned to baseline airway mechanics and AHR upon the day 51 ascaris challenge.

Example 11. Aerosolized Administration of MUC5AC RNAi Agents in Sheep.

[0381] The sheep model of allergic asthma airway inflammation described in example 10, above, was used. Three (3) ascaris sensitive sheep with previously established responses to *Ascaris suum* challenge were administered 1 mg/kg pulmonary deposited dose levels of AC000482 on days 1, 8 and 15. The chemical structure of AC000482 is shown, for example, in Table 11 and is designed to target position 3535 on the MUC5AC gene. On day 21, AHR was assessed by determining the cumulative carbachol concentration (in breath units, BU) that increased R_L to 400% over the post-1x PBS value (PC₄₀₀). On day 22, sheep were challenged with *Ascaris suum* extract, and R_L was monitored out to 8h post-challenge. On day 23, AHR was again assessed as on day 21.

[0382] Table 27. Airway Mechanics Results

Timepoint	Control (no treatment)						Drug Trial: Day 22					
	Animal #			Mean			Animal #			Mean		
	2485	2515	2535	Mean	S.D.		2485	2515	2535	Mean	S.D.	
Baseline	RL	0.99	1.00	1.00	1.00		1.00	1.00	1.00	1.00	0.00	
Post-Ascaris	RL	6.43	6.94	6.89	6.75	0.28	5.49	6.44	6.09	6.01	0.48	
	%	549%	594%	589%	577%	24%	449%	544%	509%	501%	48%	
1h	RL	4.10	4.67	4.40	4.39	0.29	4.68	4.27	4.10	4.35	0.30	
	%	314%	367%	340%	340%	26%	368%	327%	310%	335%	30%	
2h	RL	2.62	2.51	2.64	2.59	0.07	2.81	2.10	2.05	2.32	0.43	
	%	165%	151%	164%	160%	8%	181%	110%	105%	132%	43%	
3h	RL	1.65	1.46	1.58	1.56	0.10	1.53	1.37	1.31	1.40	0.11	
	%	67%	46%	58%	57%	10%	53%	37%	31%	40%	11%	
4h	RL	1.08	1.09	1.05	1.07	0.02	1.09	1.05	1.04	1.06	0.03	
	%	9%	9%	5%	8%	2%	9%	5%	4%	6%	3%	
5h	RL	1.57	1.53	1.57	1.56	0.02	1.27	1.15	1.18	1.20	0.06	
	%	59%	53%	57%	56%	3%	27%	15%	18%	20%	6%	
6h	RL	1.87	2.10	2.03	2.00	0.12	1.42	1.32	1.23	1.32	0.10	
	%	89%	110%	103%	101%	11%	42%	32%	23%	32%	10%	
6.5h	RL	2.16	2.30	2.15	2.20	0.08	1.66	1.55	1.46	1.56	0.10	
	%	118%	130%	115%	121%	8%	66%	55%	46%	56%	10%	
7h	RL	2.20	2.21	2.23	2.21	0.02	1.54	1.41	1.34	1.43	0.10	
	%	122%	121%	123%	122%	1%	54%	41%	34%	43%	10%	
7.5h	RL	2.27	2.11	2.19	2.19	0.08	1.33	1.24	1.18	1.25	0.08	
	%	129%	111%	119%	120%	9%	33%	24%	18%	25%	8%	
8h	RL	2.10	2.06	2.14	2.10	0.04	1.25	1.16	1.23	1.21	0.05	
	%	112%	106%	114%	111%	4%	25%	16%	23%	21%	5%	

[0383] Table 28: AHR results

Sheep #	BU Carbachol to Produce PC400	
	Control Trial	
	24h pre-ascaris	24h post Ascaris
2485	13	6
2515	22	12
2535	14	6
Drug Trial: Day 22		
	24h pre-ascaris	24h post Ascaris
2485	13	12
2515	24	24
2535	11	11

[0384] As shown in Table 27, treatment with AC000482 resulted in minimal attenuation of AR but robust attenuation of LR upon challenge on day 22. For example, untreated sheep display a mean LR increase of 121% in R_L at 6.5h compared to baseline, where AC000482 treated sheep on day 22 challenge show a more attenuated LR increase of 56% in R_L at 6.5h compared to baseline. In addition, 24h after the day 22 ascaris challenge all AC000482 treated sheep showed no signs of ascaris induced airway hyperresponsiveness, as shown by equivalent number of carbachol breath units required to produce PC₄₀₀. In contrast, in the control trial without AC000482 treatment, sheep required approximately half the amount of carbachol breath units to induce PC₄₀₀ post-ascaris challenge, signifying airway hyperresponsiveness.

Example 12. Aerosolized Administration of MUC5AC RNAi Agents in Sheep.

[0385] The sheep model of allergic asthma airway inflammation described in example 10, above, was used. Six (6) ascaris sensitive sheep with previously established responses to *Ascaris suum* challenge were administered either 0.5 mg/kg pulmonary deposited dose levels of AC000482 (n=3) or 0.25 mg/kg pulmonary deposited dose levels of AC000482 on days 1, 8 and 15. On day 21, AHR was assessed by determining the cumulative carbachol concentration (in breath units, BU) that increased R_L to 400% over the post-1x PBS value (PC₄₀₀). On day 22, sheep were challenged with *Ascaris suum* extract, and R_L was monitored out to 8h post-challenge. On day 23, AHR was again assessed as on day 21.

[0386] Table 29. Airway mechanics results, 0.5 mg/kg dose level

Timepoint		Control (no treatment)				Drug Trial: Day 22			
		Animal #		Mean		Animal #		Mean	
		2489	2497	2520	Mean	S.D.	2489	2497	2520
Baseline	RL	0.99	0.99	0.99	0.99	0.00	1.00	1.00	1.00
Post-Ascaris	RL	6.66	6.62	7.37	6.88	0.42	6.23	6.38	7.10
	%	573%	569%	644%	595%	43%	523%	538%	610%
1h	RL	4.51	4.40	4.49	4.47	0.06	4.15	4.06	4.33
	%	356%	344%	354%	351%	6%	315%	306%	333%
2h	RL	2.53	2.57	2.37	2.49	0.11	2.25	2.31	2.10
	%	156%	160%	139%	152%	11%	125%	131%	110%
3h	RL	1.55	1.53	1.53	1.54	0.01	1.41	1.46	1.35
	%	57%	55%	55%	55%	1%	41%	46%	35%
4h	RL	1.06	1.21	1.12	1.13	0.08	1.07	1.02	1.04
	%	7%	22%	13%	14%	8%	7%	2%	4%
5h	RL	1.52	1.66	1.54	1.57	0.08	1.21	1.33	1.38
	%	54%	68%	56%	59%	8%	21%	33%	38%
6h	RL	2.13	2.09	2.03	2.08	0.05	1.46	1.56	1.52
	%	115%	111%	105%	110%	5%	46%	56%	52%
6.5h	RL	2.26	2.21	2.21	2.23	0.03	1.68	1.72	1.67
	%	128%	123%	123%	125%	3%	68%	72%	67%
7h	RL	2.32	2.26	2.30	2.29	0.03	1.62	1.68	1.61
	%	134%	128%	132%	132%	3%	62%	68%	61%
7.5h	RL	2.12	2.16	2.20	2.16	0.04	1.30	1.41	1.48
	%	114%	118%	122%	118%	4%	30%	41%	48%
8h	RL	2.08	2.03	2.12	2.08	0.05	1.25	1.26	1.13
	%	110%	105%	114%	110%	5%	25%	26%	13%

[0387] Table 30: Airway mechanics results, 0.25 mg/kg dose level

Timepoint		Control (no treatment)				Drug Trial: Day 22			
		Animal #		Mean		Animal #		Mean	
		2457	2517	2539	S.D.	2457	2517	2539	S.D.
Baseline	RL	1.00	1.01	1.00	0.01	1.00	1.00	1.00	0.00
Post-Ascaris	RL	6.63	7.29	6.03	6.65	6.50	7.03	6.26	6.60
	%	563%	622%	503%	563%	550%	603%	526%	560%
1h	RL	4.15	4.26	4.50	4.30	4.09	4.10	4.11	4.10
	%	315%	322%	350%	329%	309%	310%	311%	310%
2h	RL	2.73	2.47	2.59	2.60	2.23	2.33	2.46	2.34
	%	173%	145%	159%	159%	123%	133%	146%	134%
3h	RL	1.54	1.37	1.62	1.51	1.45	1.27	1.54	1.42
	%	54%	36%	62%	51%	45%	27%	54%	42%
4h	RL	1.17	1.08	1.03	1.09	1.07	1.03	1.04	1.05
	%	17%	7%	3%	9%	7%	3%	4%	5%
5h	RL	1.69	1.61	1.29	1.53	1.43	1.21	1.32	1.32
	%	69%	59%	29%	52%	43%	21%	32%	32%
6h	RL	2.04	2.14	2.26	2.15	1.62	1.51	1.57	1.57
	%	104%	112%	126%	114%	62%	51%	57%	57%
6.5h	RL	2.18	2.36	2.14	2.23	1.87	1.78	1.83	1.83
	%	118%	134%	114%	122%	87%	78%	83%	83%
7h	RL	2.12	2.52	2.30	2.31	1.93	1.89	1.86	1.89
	%	112%	150%	130%	131%	93%	89%	86%	89%
7.5h	RL	2.17	2.35	2.21	2.24	1.74	1.67	1.68	1.70
	%	117%	133%	121%	124%	74%	67%	68%	70%
8h	RL	2.18	2.30	2.17	2.22	1.52	1.45	1.55	1.51
	%	118%	128%	117%	121%	52%	45%	55%	51%

[0388] Table 31: AHR results, 0.5 mg/kg dose level

Sheep #	BU Carbachol to Produce PC400	
	Control Trial	
	24h pre-ascaris	24h post Ascaris
2489	24	13
2497	31	13
2520	26	13
Drug Trial: Day 22		
	24h pre-ascaris	24h post Ascaris
2489	26	25
2497	26	24
2520	27	25

[0389] Table 32: AHR results, 0.25 mg/kg dose level

Sheep #	BU Carbachol to Produce PC400	
	Control Trial	
	24h pre-ascaris	24h post Ascaris
2457	10	6
2517	28	13
2539	13	6
Drug Trial: Day 22		
	24h pre-ascaris	24h post Ascaris
2457	13	11
2517	26	25
2539	14	13

[0390] As shown in Table 29, treatment with AC000482 at 0.5 mg/kg dose level resulted in minimal attenuation of AR but robust attenuation of LR upon challenge on day 22. For example, untreated sheep display a mean LR increase of 125% in R_L at 6.5h compared to baseline, where AC000482 treated sheep on day 22 challenge show a more attenuated LR increase of 69% in R_L at 6.5h compared to baseline. In addition, 24h after the day 22 ascaris challenge all AC000482 treated sheep showed no signs of ascaris induced airway hyperresponsiveness, as shown by similar number of carbachol breath units required to produce PC₄₀₀. In contrast, in the control trial without AC000482 treatment, sheep required approximately half the amount of carbachol breath units to induce PC₄₀₀ post-ascaris challenge, signifying airway hyperresponsiveness.

[0391] As shown in Table 30, treatment with AC000482 at 0.25 mg/kg dose level resulted in minimal attenuation of AR but robust attenuation of LR upon challenge on day 22. For example, untreated sheep display a mean LR increase of 122% in R_L at 6.5h compared to

baseline, where AC000482 treated sheep on day 22 challenge show a more attenuated LR increase of 83% in R_L at 6.5h compared to baseline. In addition, 24h after the day 22 ascaris challenge all AC000482 treated sheep showed no signs of ascaris induced airway hyperresponsiveness, as shown by similar number of carbachol breath units required to produce PC_{400} . In contrast, in the control trial without AC000482 treatment, sheep required approximately half the amount of carbachol breath units to induce PC_{400} post-ascaris challenge, signifying airway hyperresponsiveness.

[0392] Collectively, the results demonstrate dose-responsive impacts of AC000482 treatment on airway mechanics following ascaris challenge. The results show that even at the lowest dose of AC000482, the impact on the late phase response is still substantial enough to block airway hyperresponsiveness 24h post challenge.

Example 13. Aerosolized Administration of MUC5AC RNAi Agents in Sheep.

[0393] The sheep model of allergic asthma airway inflammation described in example 10, above, was used. Six (6) ascaris sensitive sheep with previously established responses to *Ascaris suum* challenge were administered, on days 1, 8 and 15, with either 1.0 mg/kg pulmonary deposited dose levels of AC000480 or 1.0 mg/kg pulmonary deposited dose of a negative control siRNA conjugate that included the same targeting ligand but is unable to load into the RISC complex and therefore is unable to mediate RNA interference gene silencing. On day 21, AHR was assessed by determining the cumulative carbachol concentration (in breath units, BU) that increased R_L to 400% over the post-1x PBS value (PC_{400}). On day 22, sheep were challenged with *Ascaris suum* extract, and R_L was monitored out to 8h post-challenge. On day 23, AHR was again assessed as on day 21. Sheep dosed with AC000480 attenuated allergen-induced late-phase reaction and airway hyperresponsiveness in a dose dependent manner, while similar exposure of the negative control conjugate did not attenuate allergen-induced changes in airway mechanics.

OTHER EMBODIMENTS

[0394] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit

the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

Claims:

1. An RNAi agent for inhibiting expression of a Mucin 5AC gene, comprising:
an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2 or Table 3; and
a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.
2. The RNAi agent of claim 1, wherein the antisense strand comprises nucleotides 2-18 of any one of the sequences provided in Table 2 or Table 3.
3. The RNAi agent of claim 1 or claim 2, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2 or Table 4, and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.
4. The RNAi agent of any one of claims 1-3, wherein at least one nucleotide of the RNAi agent is a modified nucleotide or includes a modified internucleoside linkage.
5. The RNAi agent of any one of claims 1-4, wherein all or substantially all of the nucleotides are modified nucleotides.
6. The RNAi agent of any one of claims 4-5, wherein the modified nucleotide is selected from the group consisting of: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2',3'-seco nucleotide mimic, locked nucleotide, 2'-F-arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted 2'-O-methyl nucleotide, inverted 2'-deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, vinyl phosphonate-containing nucleotide, cyclopropyl phosphonate-containing nucleotide, and 3'-O-methyl nucleotide.
7. The RNAi agent of claim 5, wherein all or substantially all of the nucleotides are modified with 2'-O-methyl nucleotides, 2'-fluoro nucleotides, or combinations thereof.
8. The RNAi agent of any one of claims 1-7, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3 or Table 11.

9. The RNAi agent of any one of claims 1-8, wherein the sense strand comprises the nucleotide sequence of any one of the modified sense strand sequences provided in Table 4 or Table 11.
10. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence of any one of the modified antisense strand sequences provided in Table 3 or Table 11, and the sense strand comprises the nucleotide sequence of any one of the modified sense strand sequences provided in Table 4 or Table 11.
11. The RNAi agent of any one of claims 1-10, wherein the sense strand is between 18 and 30 nucleotides in length, and the antisense strand is between 18 and 30 nucleotides in length.
12. The RNAi agent of claim 11, wherein the sense strand and the antisense strand are each between 18 and 27 nucleotides in length.
13. The RNAi agent of claim 12, wherein the sense strand and the antisense strand are each between 18 and 24 nucleotides in length.
14. The RNAi agent of claim 13, wherein the sense strand and the antisense strand are each 21 nucleotides in length.
15. The RNAi agent of claim 14, wherein the RNAi agent has two blunt ends.
16. The RNAi agent of any one of claims 1-15, wherein the sense strand comprises one or two terminal caps.
17. The RNAi agent of any one of claims 1-16, wherein the sense strand comprises one or two inverted abasic residues.
18. The RNAi agent of claim 1, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex having the structure of any one of the duplexes in Table 8A, Table 8B, Table 8C, Table 9, Table 10A, or Table 10B.
19. The RNAi agent of claim 18, wherein all or substantially all of the nucleotides are modified nucleotides.
20. The RNAi agent of claim 1, wherein the antisense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5' → 3'):

UUGUAGUAGUCGCAGAACA (SEQ ID NO:79); or
UUCUUGUUCAGGCAAAUCA (SEQ ID NO:83).

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

UUGUAGUAGUCGACAGAACAGC (SEQ ID NO:1525); or

UUCUUGUUCAGGCAAAUCAGC (SEQ ID NO:1535).

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

UGUUCUGCGACUACUACAA (SEQ ID NO:568); or

UGAUUUGCCUGAACAAGAA (SEQ ID NO:572).

23. The RNAi agent of claim 20, 21, or 22, wherein all or substantially all of the nucleotides are modified nucleotides.

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

cPrpusUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1127);

usUfsgsUfaGfuAfgUfcGfcAfgAfaCfaGfsc (SEQ ID NO:1065);

usUfscsuuguucagGfcAfaAfucagsc (SEQ ID NO:1166); or

cPrpuUfcuuguucagGfcAfaAfucagsc (SEQ ID NO:1191);

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

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

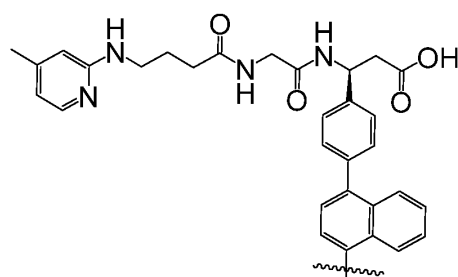
gscuguucuGfCfGfacuacuacaa (SEQ ID NO:1265); or

gscugauUfuGfcCfugaacaagaa (SEQ ID NO:1315);

wherein a, c, g, and u represent 2'-O-methyl adenosine, 2'-O-methyl cytidine, 2'-O-methyl guanosine, and 2'-O-methyl uridine, respectively; Af, Cf, Gf, and Uf represent 2'-fluoro

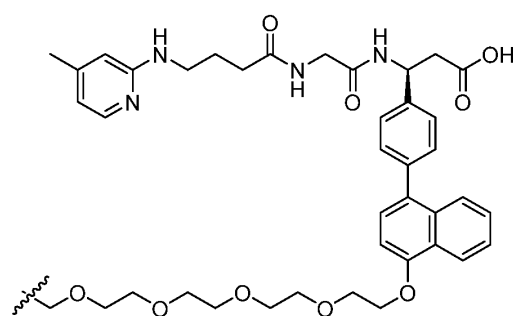
adenosine, 2'-fluoro cytidine, 2'-fluoro guanosine, and 2'-fluoro uridine, respectively; and s represents a phosphorothioate linkage; and wherein all or substantially all of the nucleotides on the antisense strand are modified nucleotides.

26. The RNAi agent of any one of claims 20-25, wherein the sense strand further includes inverted abasic residues at the 3' terminal end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both.
27. The RNAi agent of any one of claims 1-26, wherein the RNAi agent is linked to a targeting ligand.
28. The RNAi agent of claim 27, wherein the targeting ligand has affinity for a cell receptor expressed on an epithelial cell.
29. The RNAi agent of claim 28, wherein the targeting ligand comprises an integrin targeting ligand.
30. The RNAi agent of claim 29, wherein the integrin targeting ligand is an $\alpha v\beta 6$ integrin targeting ligand.
31. The RNAi agent of claim 30, wherein the targeting ligand comprises the structure:



or a pharmaceutically acceptable salt

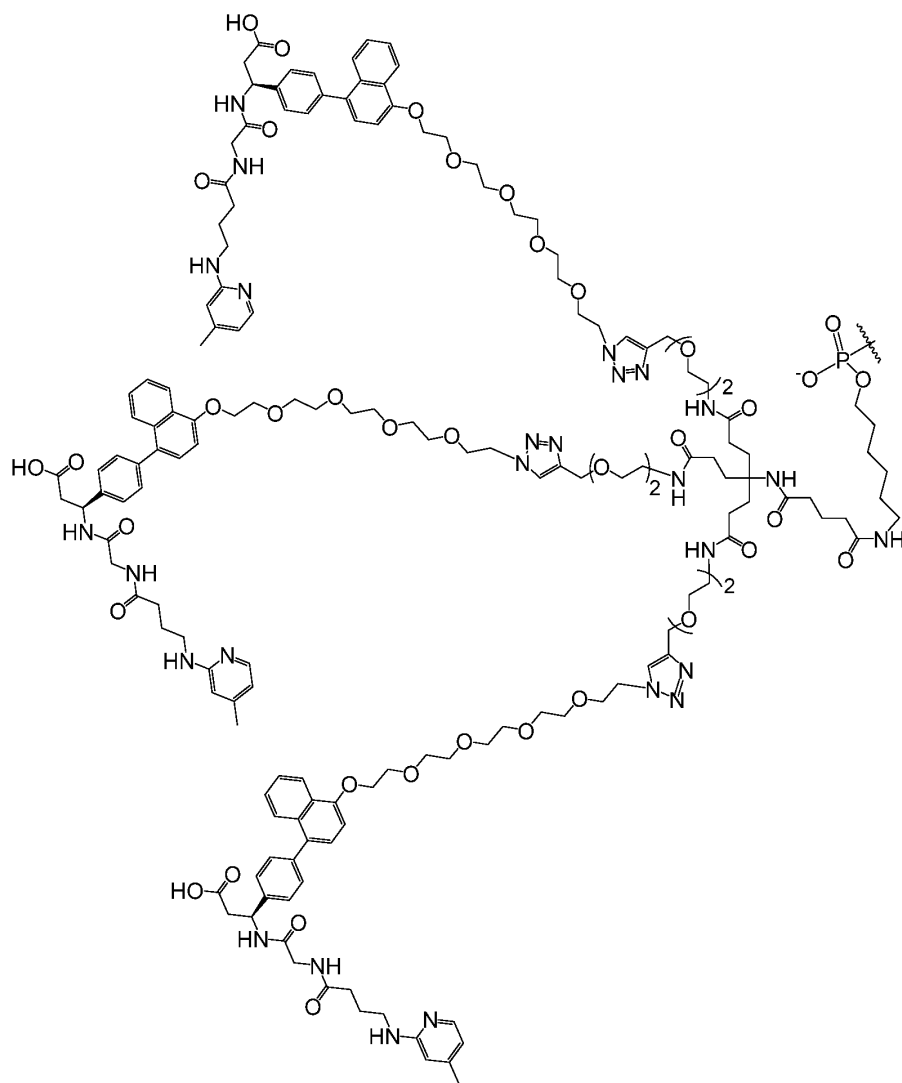
thereof, or



or a pharmaceutically acceptable salt

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

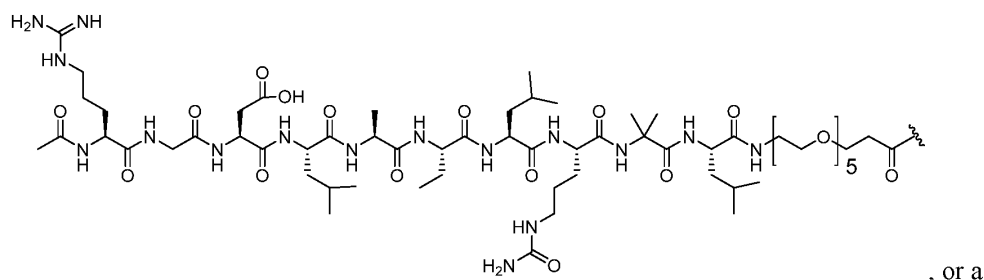
32. The RNAi agent of any one of claims 27-30, wherein RNAi agent is conjugated to a targeting ligand having the following structure:



, or a

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

33. The RNAi agent of any one of claims 27-30, wherein the targeting ligand has the following structure:



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

34. The RNAi agent of any one of claims 27-33, wherein the targeting ligand is conjugated to the sense strand.
35. The RNAi agent of claim 34, wherein the targeting ligand is conjugated to the 5' terminal end of the sense strand.
36. A composition comprising the RNAi agent of any one of claims 1-35, wherein the composition further comprises a pharmaceutically acceptable excipient.
37. The composition of claim 36, further comprising a second RNAi agent capable of inhibiting the expression of Mucin 5AC gene expression.
38. The composition of any one of claims 36-37, further comprising one or more additional therapeutics.
39. The composition of any one of claims 36-38, wherein the composition is formulated for administration by inhalation.
40. The composition of claim 39, wherein the composition is delivered by a metered-dose inhaler, jet nebulizer, vibrating mesh nebulizer, or soft mist inhaler.
41. The composition of any of claims 36-40, wherein the RNAi agent is a sodium salt.
42. The composition of any of claims 36-41, wherein the pharmaceutically acceptable excipient is water for injection.
43. The composition of any of claims 36-42, wherein the pharmaceutically acceptable excipient is isotonic saline.
44. A method for inhibiting expression of a MUC5AC gene in a cell, the method comprising introducing into a cell an effective amount of an RNAi agent of any one of claims 1-35 or the composition of any one of claims 36-43.
45. The method of claim 44, wherein the cell is within a subject.

46. The method of claim 45, wherein the subject is a human subject.
47. The method of any one of claims 44-46, wherein following the administration of the RNAi agent the Mucin 5AC gene expression is inhibited by at least about 30%.
48. A method of treating one or more symptoms or diseases associated with MUC5AC protein levels, the method comprising administering to a human subject in need thereof a therapeutically effective amount of the composition of any one of claims 36-43.
49. The method of claim 48, wherein the disease is a mucoobstructive lung disease.
50. The method of claim 49, wherein the mucoobstructive lung disease is asthma (including severe asthma), cystic fibrosis (CF), bronchiectasis (NCFB), or chronic obstructive pulmonary disease (COPD).
51. The method of claim 50, wherein the disease is asthma (including severe asthma).
52. The method of claim 48, wherein the disease is cancer.
53. The method of claim 52, wherein the cancer is lung adenocarcinoma, pancreatic cancer, salivary gland carcinoma, breast cancer, cholangiocarcinoma, or ovarian cancer.
54. The method of any one of claims 44-53, wherein the RNAi agent is administered at a pulmonary deposited dose (PDD) of about 0.01 mg/kg to about 5.0 mg/kg of body weight of the subject.
55. The method of any one of claims 44-53, wherein the RNAi agent is administered at a pulmonary deposited dose (PDD) of about 0.1 mg/kg to about 2.0 mg/kg of body weight of the subject.
56. The method of any one of claims 44-53, wherein the RNAi agent is administered at a respirable delivered dose (RDD) of about 0.01 mg/kg to about 5.0 mg/kg of body weight of the subject.
57. The method of any one of claims 44-53, wherein the RNAi agent is administered at a respirable delivered dose (RDD) of about 0.1 mg/kg to about 2.0 mg/kg of body weight of the subject.
58. The method of any of claims 44-57, wherein the RNAi agent is administered in two or more doses.
59. Use of the RNAi agent of any one of claims 1-35, for the treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC protein levels.

60. Use of the composition according to any one of claims 36-43, for the treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC gene expression.
61. Use of the composition according to any one of claims 36-43, for the manufacture of a medicament for treatment of a disease, disorder, or symptom that is mediated at least in part by Mucin 5AC gene expression.
62. The use of any one of claims 59-61, wherein the disease is asthma (including severe asthma).
63. A method of making an RNAi agent of any one of claims 1-35, comprising annealing a sense strand and an antisense strand to form a double-stranded ribonucleic acid molecule.
64. The method of claim 63, wherein the sense strand comprises a targeting ligand.
65. The method of claim 64, comprising conjugating a targeting ligand to the sense strand.