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(54) **COMPOSITIONS AND METHODS OF
TREATING FACIOSCAPULOHUMERAL
MUSCULAR DYSTROPHY**

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(60) Provisional application No. 63/066,655, filed on Aug.
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Publication Classification

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C07K 19/00 (2006.01)
C07K 16/28 (2006.01)

(57)

ABSTRACT

Disclosed herein are polynucleic acid molecules, pharma-
ceutical compositions, and methods for treating Facioscapu-
lohumeral muscular dystrophy.

Specification includes a Sequence Listing.

FIG. 1

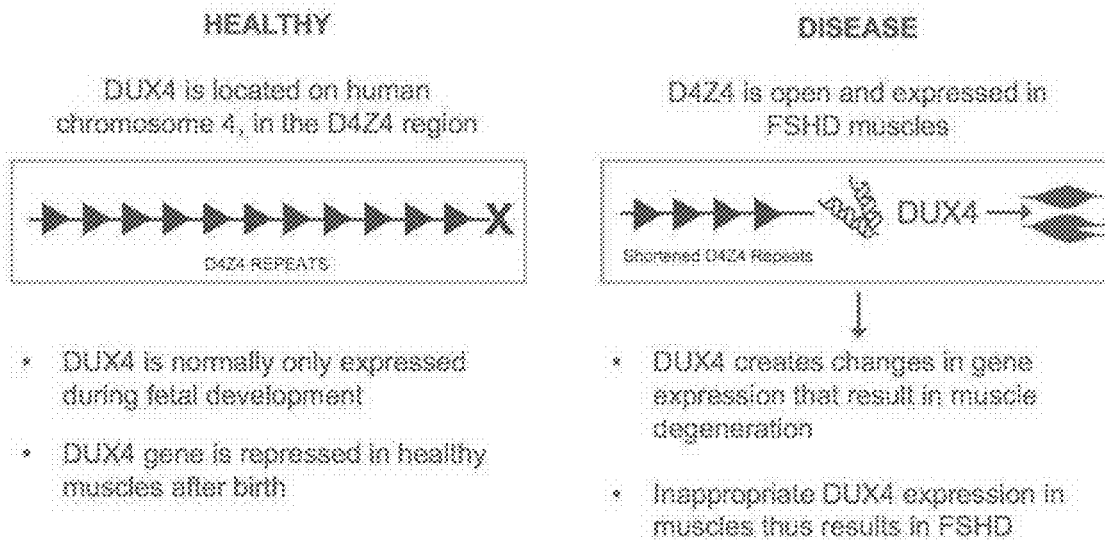


FIG. 2

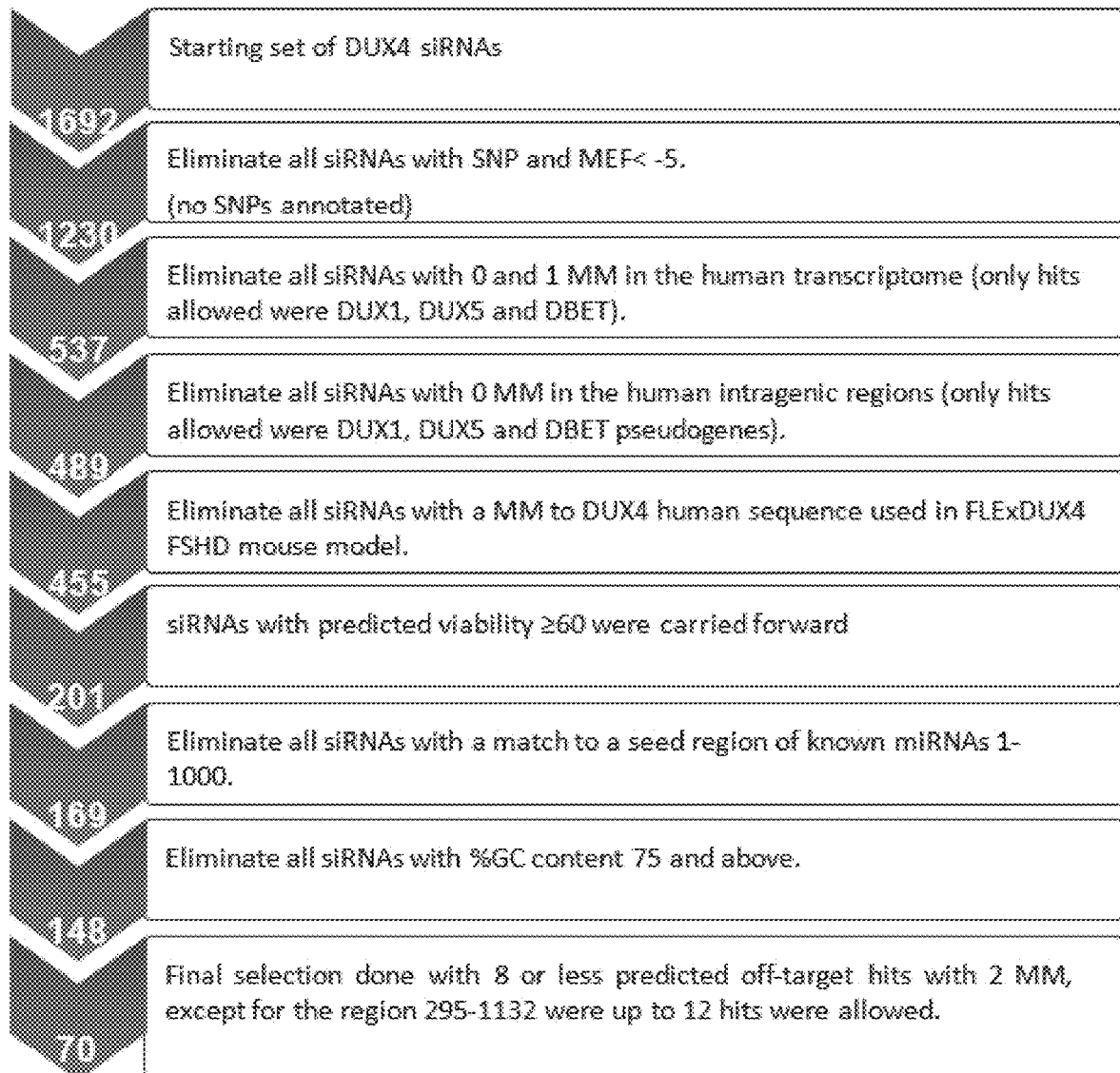


FIG. 3

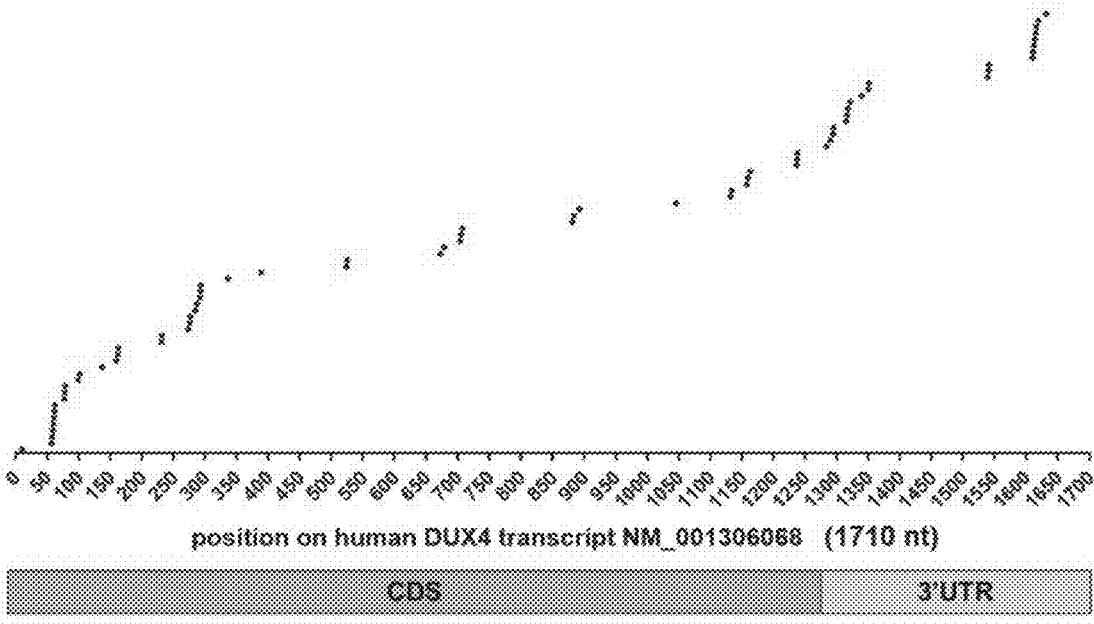


FIG. 4

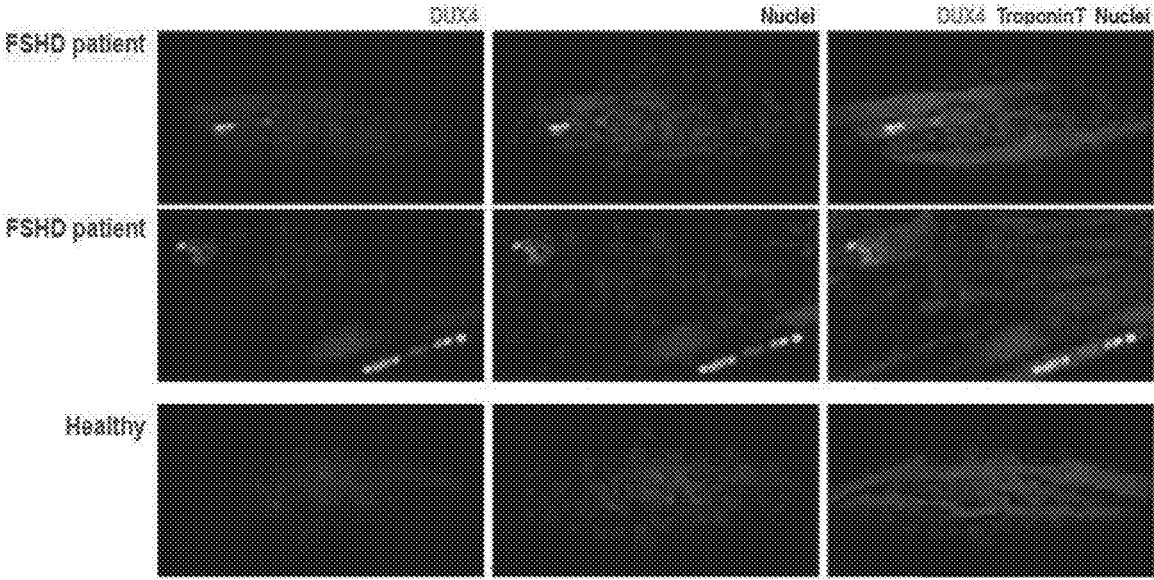


FIG. 5

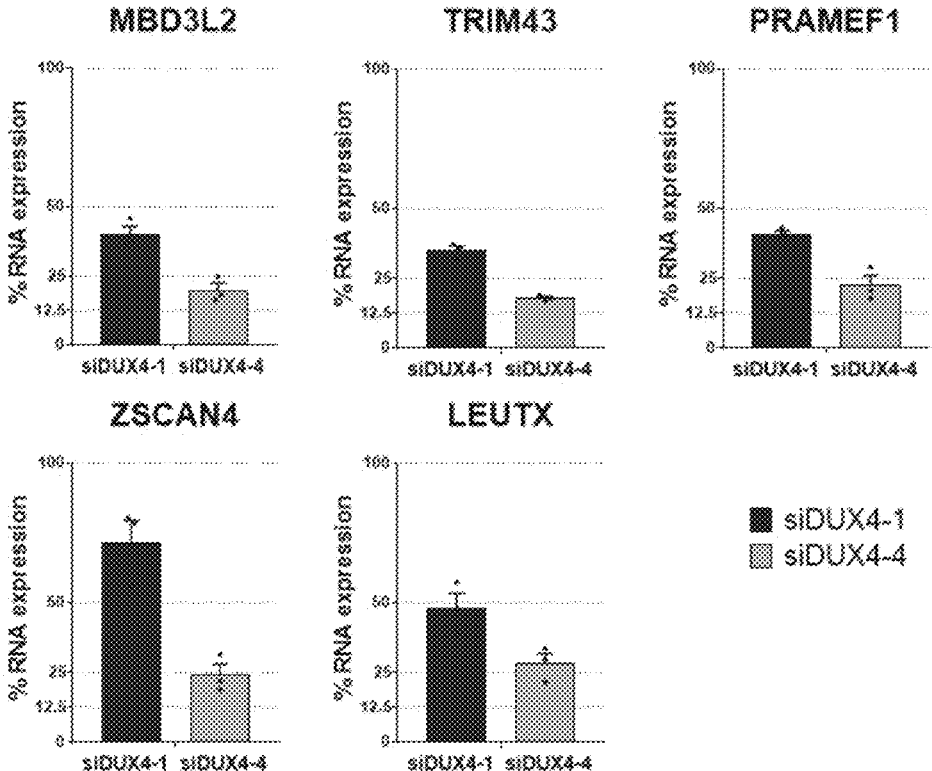


FIG. 6A

MB06

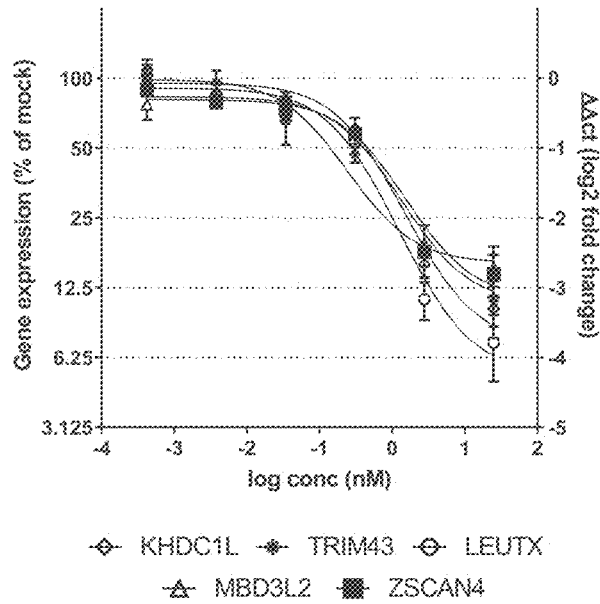
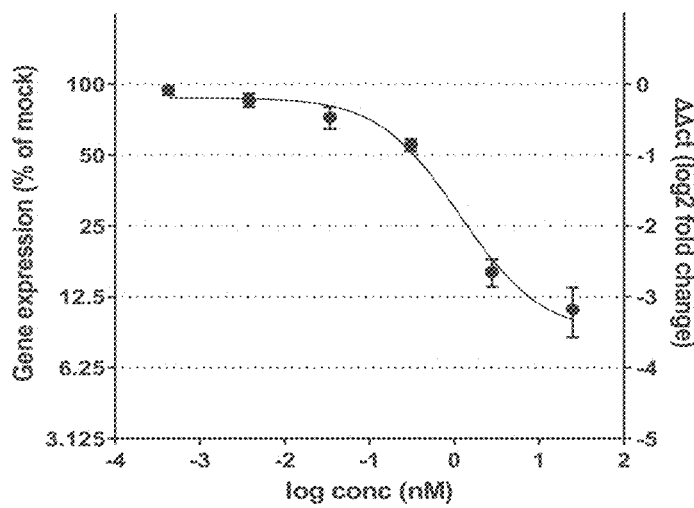


FIG. 6B

MB06



Calculations of the FSHD composite:
 Det = (Av. ct 5 DUX4 target genes) - (Av. ct 2 HKGs)
 DDet = Det (siDUX4) - Det (mock)
 Composite = $2^{-DDet} * 100$ (%)

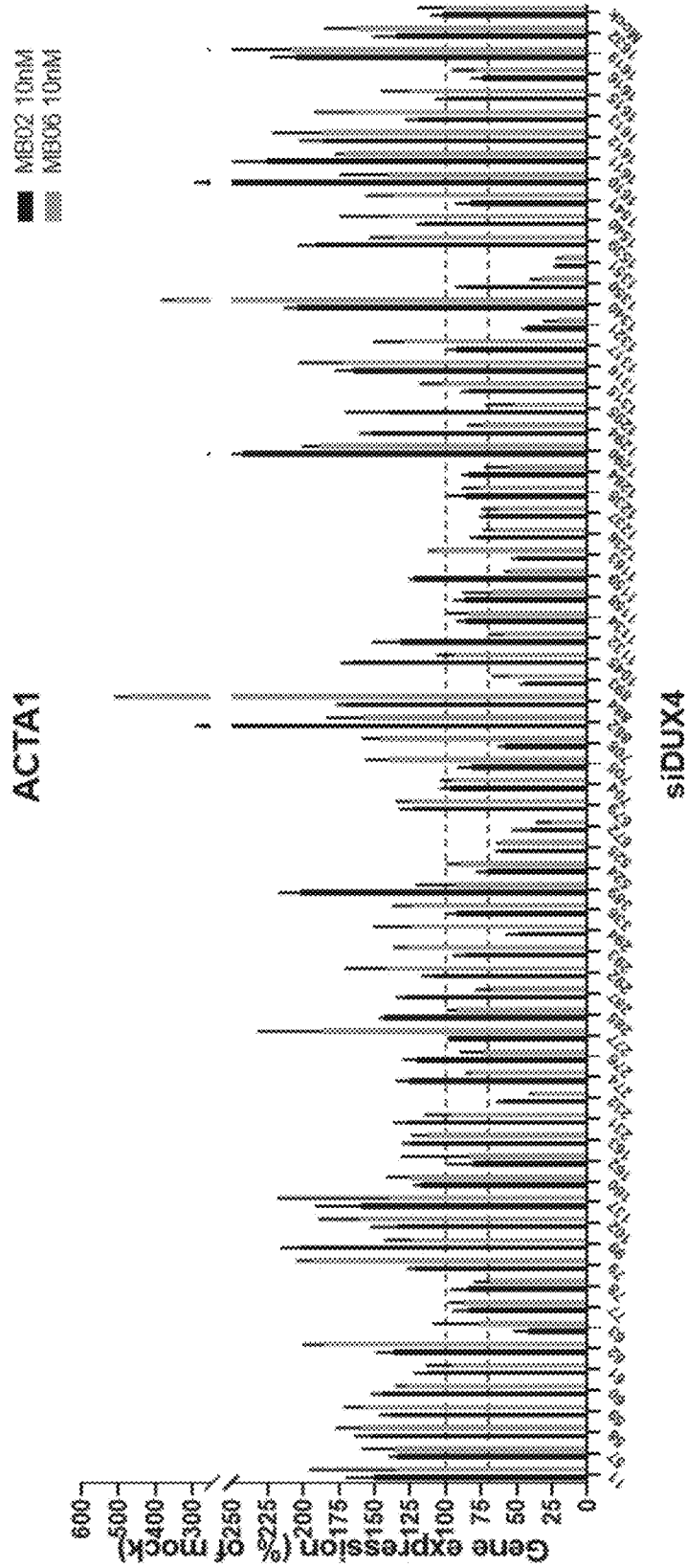


FIG. 7

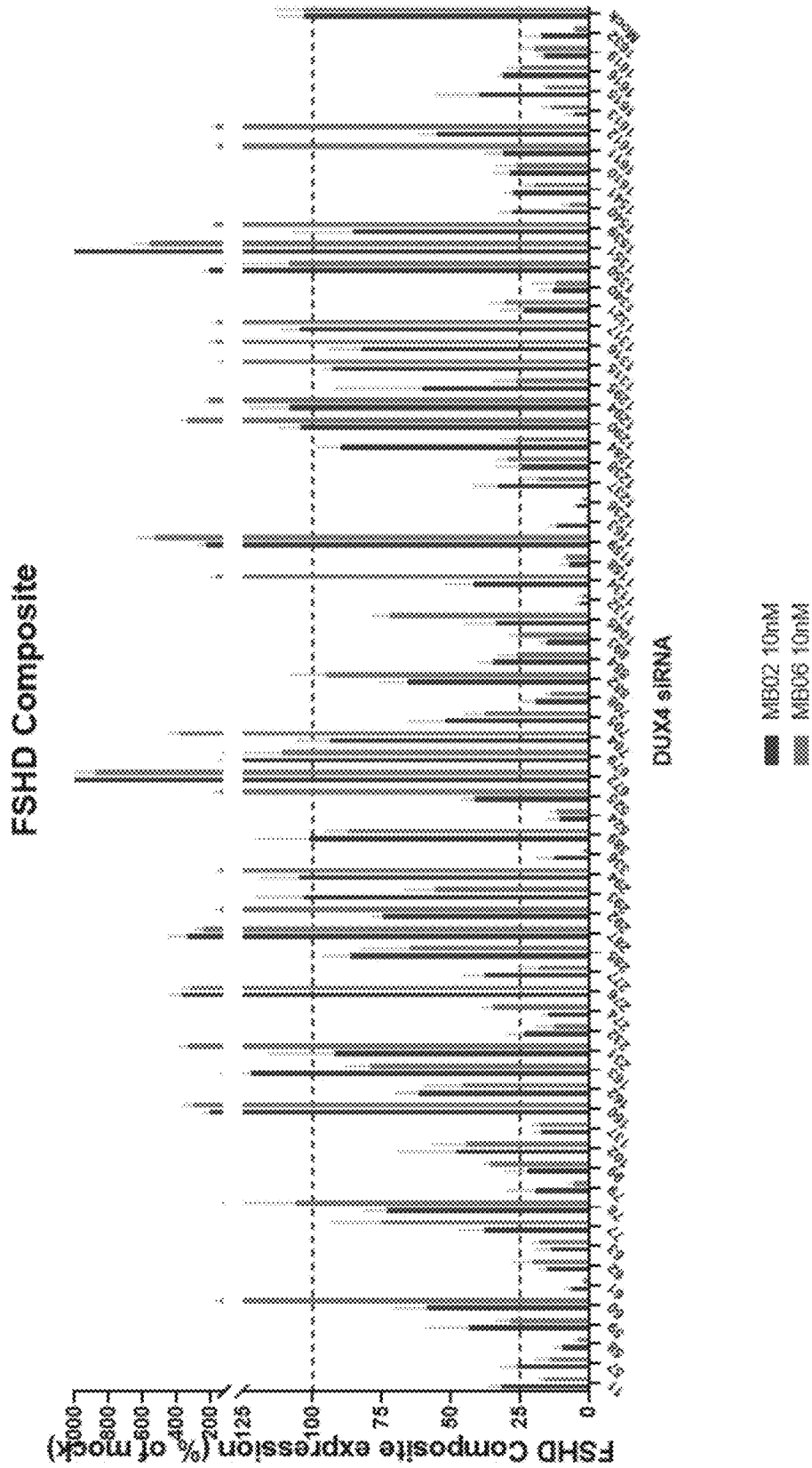


FIG. 8

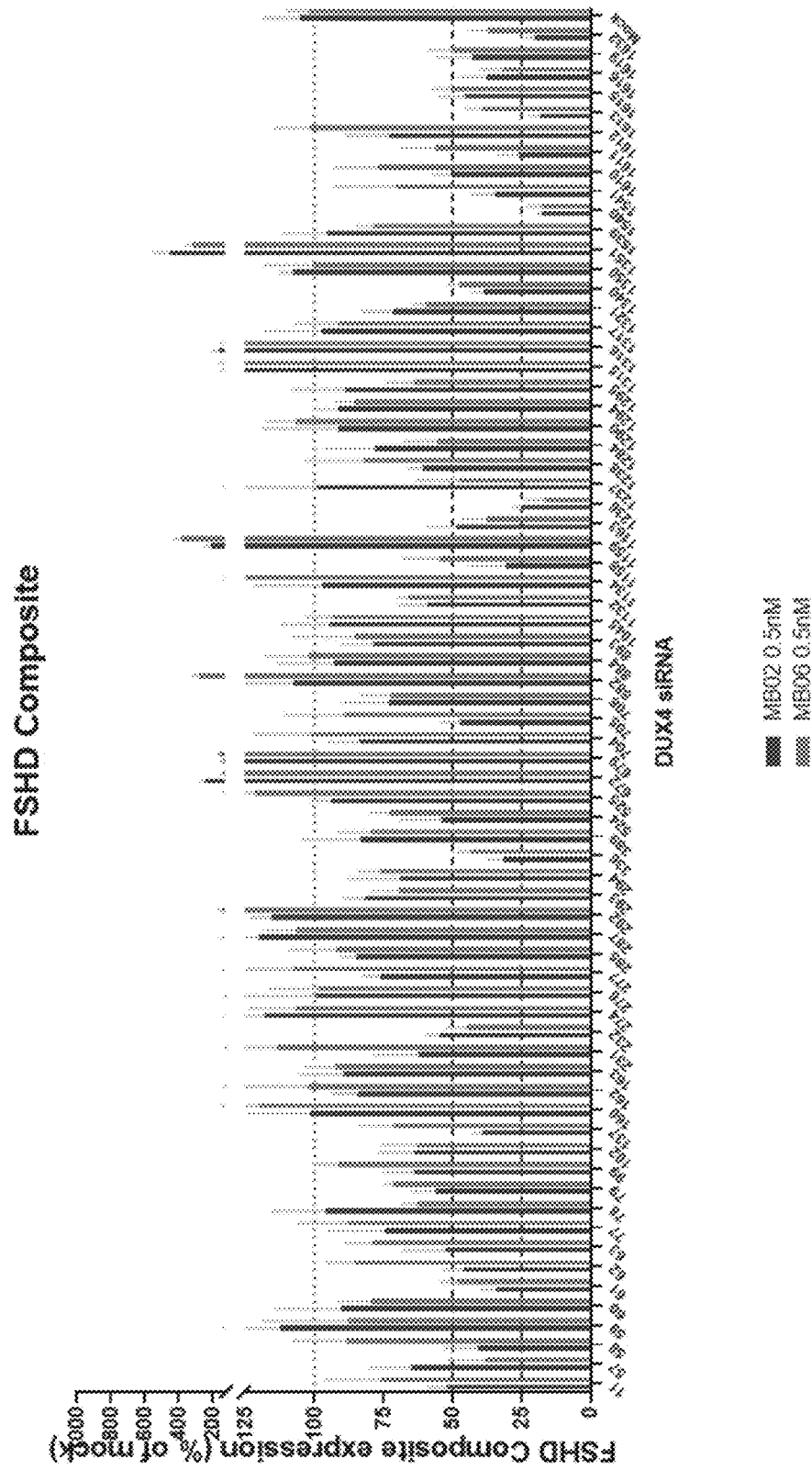


FIG. 9

FIG. 10

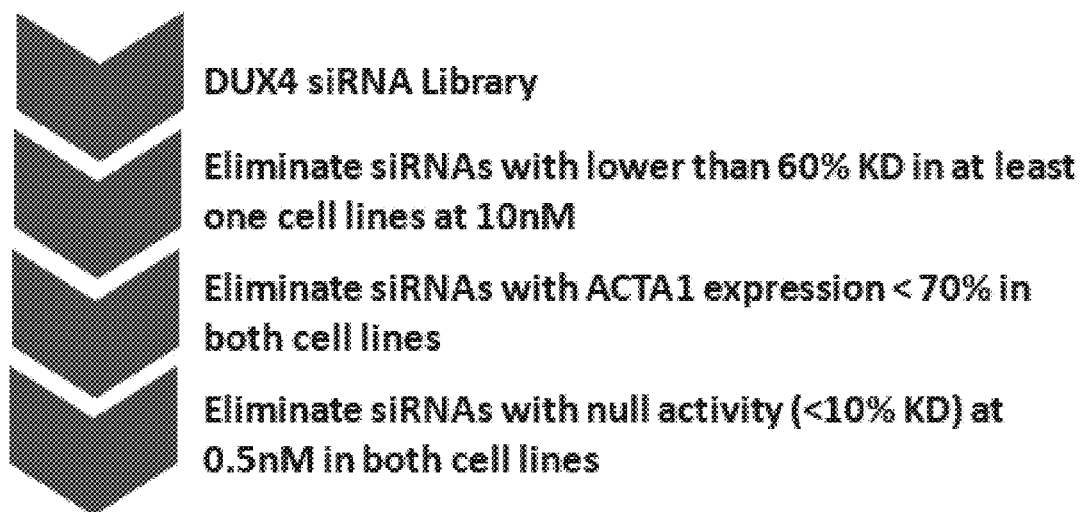


FIG. 11A

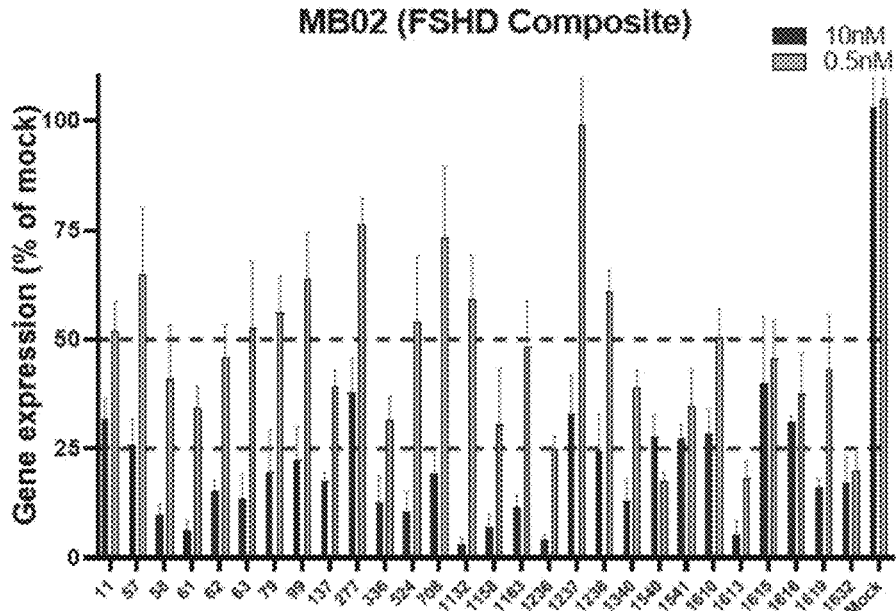
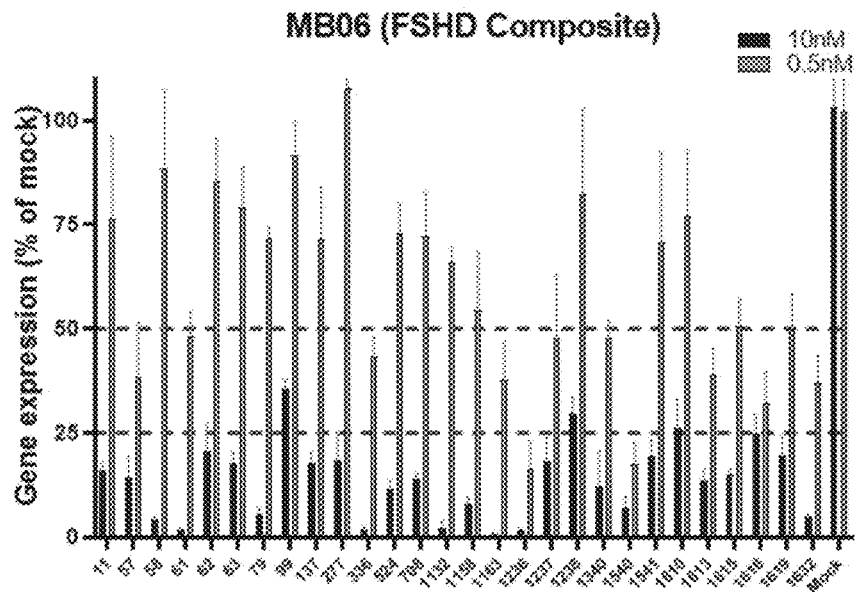


FIG. 11B



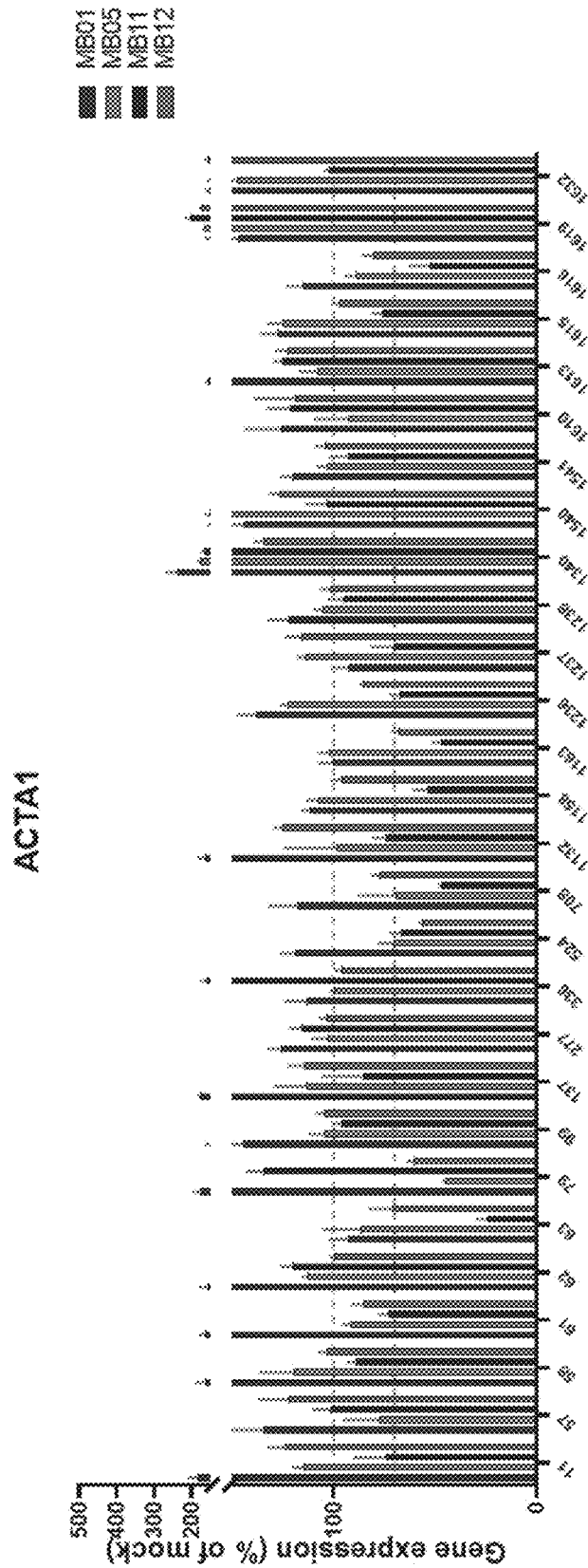
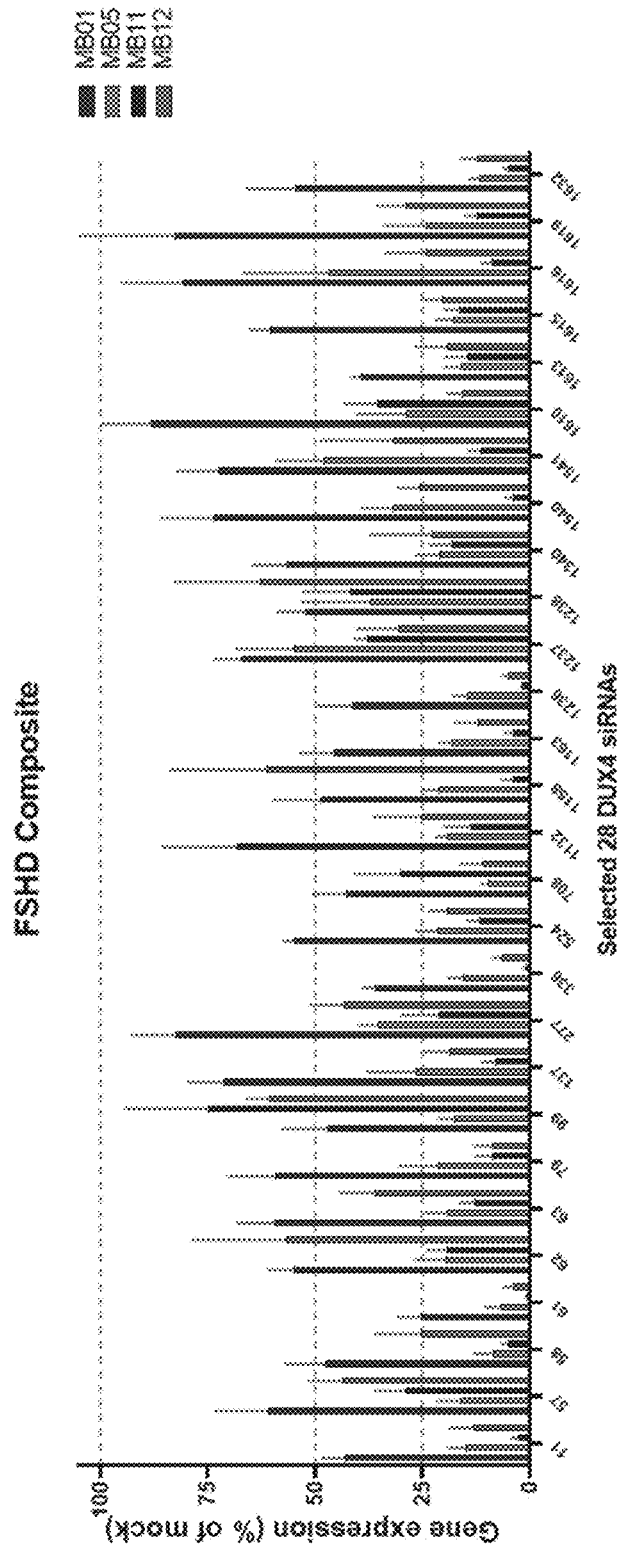


FIG. 13



Calculations for the FSHD composite:
Dot = (Av. ct 4 DUXX4 target genes) - (Av. ct 2 HKGs)
DDot = Dot (siDUXX4) - Dot (mock)
Composite = $2^{DDot} \cdot 100$ (%)

FIG. 14

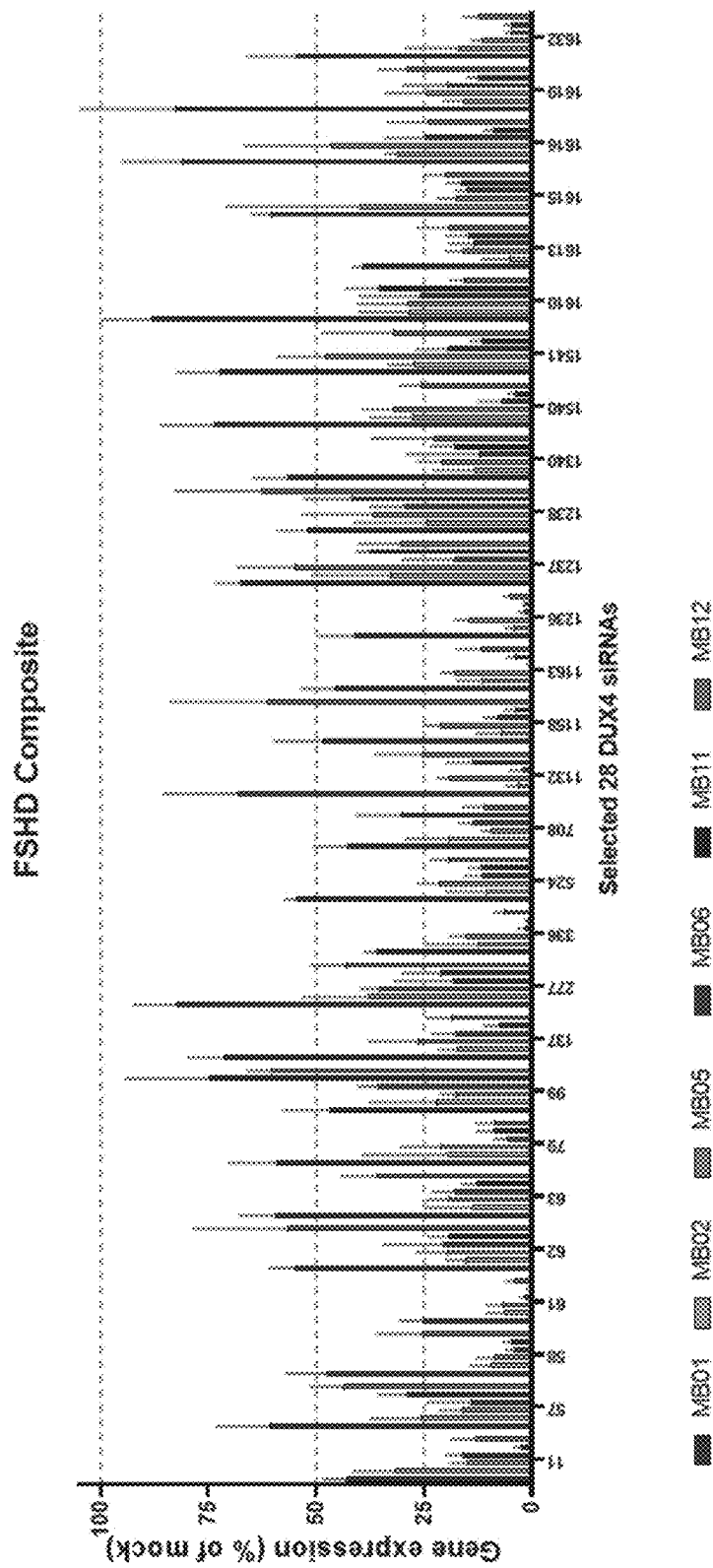


FIG. 15

FIG. 16A

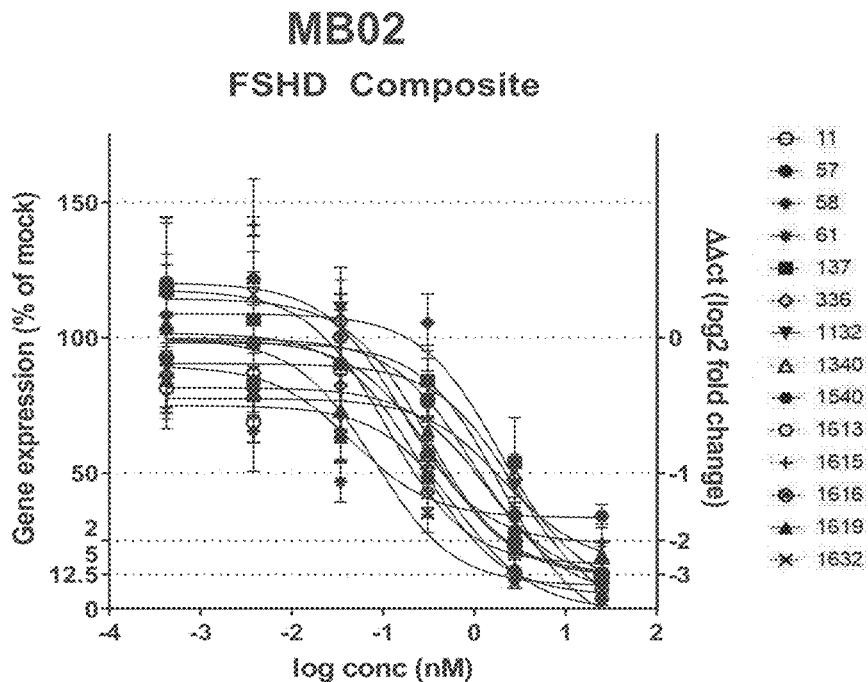


FIG. 16B

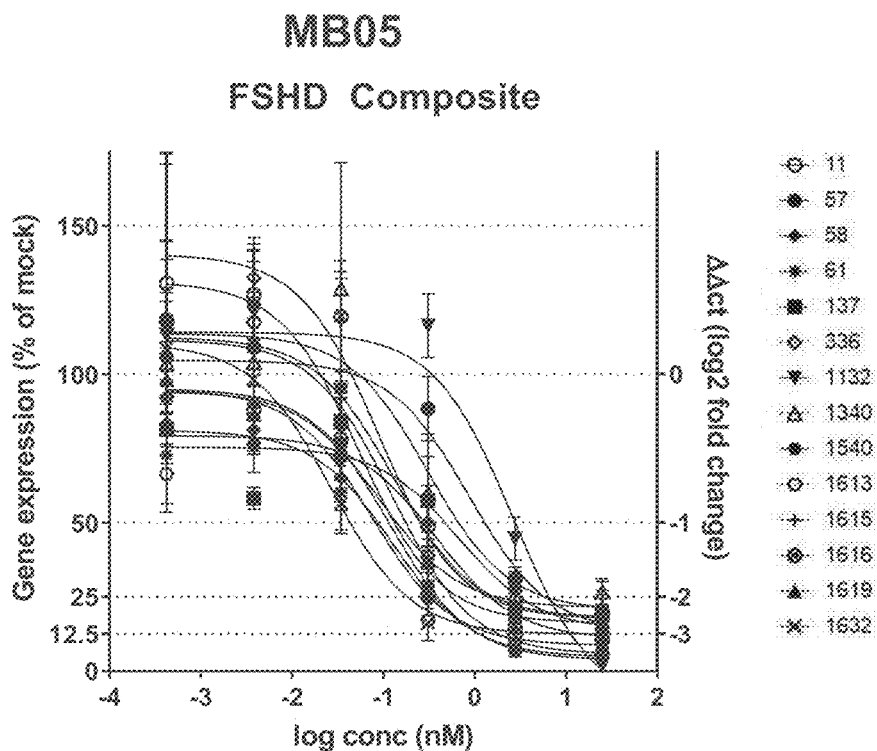
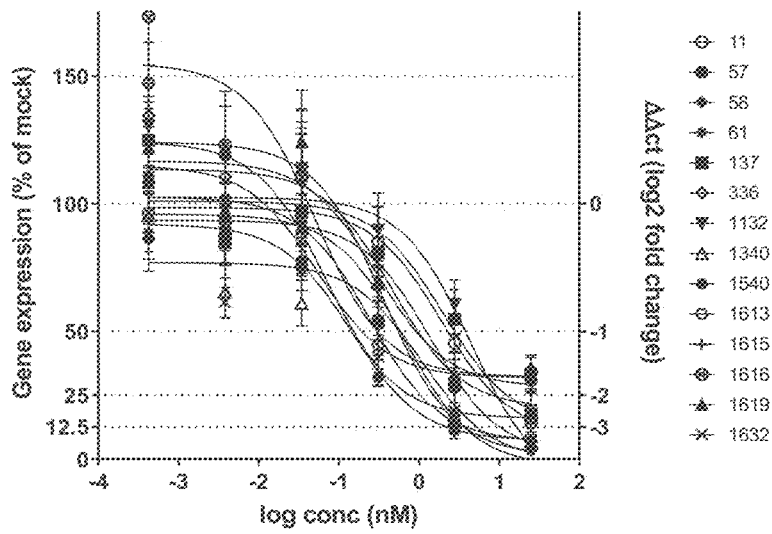


FIG. 16C

MB06
FSHD Composite



Calculations for the FSHD composite:
 $Dct = (\text{Av. ct } 4 \text{ DUX4 target genes}) - (\text{Av. ct } 2 \text{ HKGs})$
 $DDct = Dct(\text{siDUX4}) - Dct(\text{mock})$
 $\text{Composite} = 2^{-DDct} * 100 (\%)$

FIG. 17A

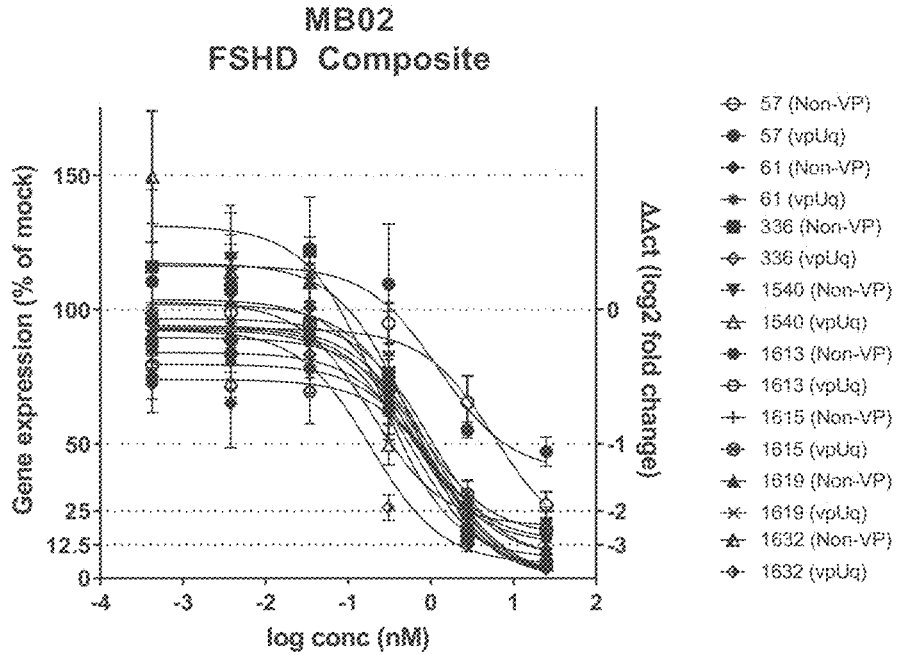


FIG. 17B

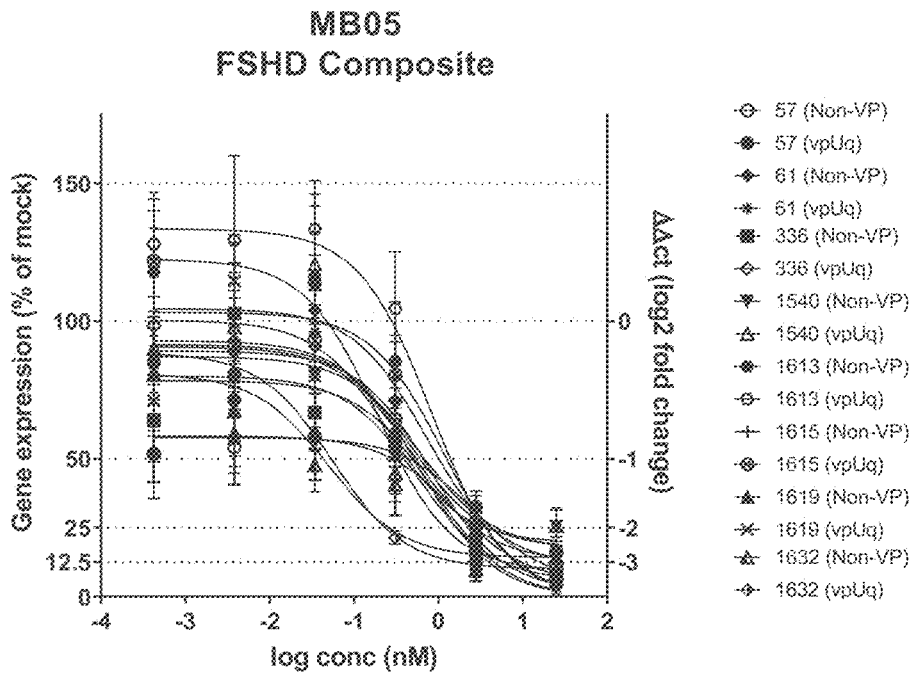


FIG. 17C

MB12
FSHD Composite

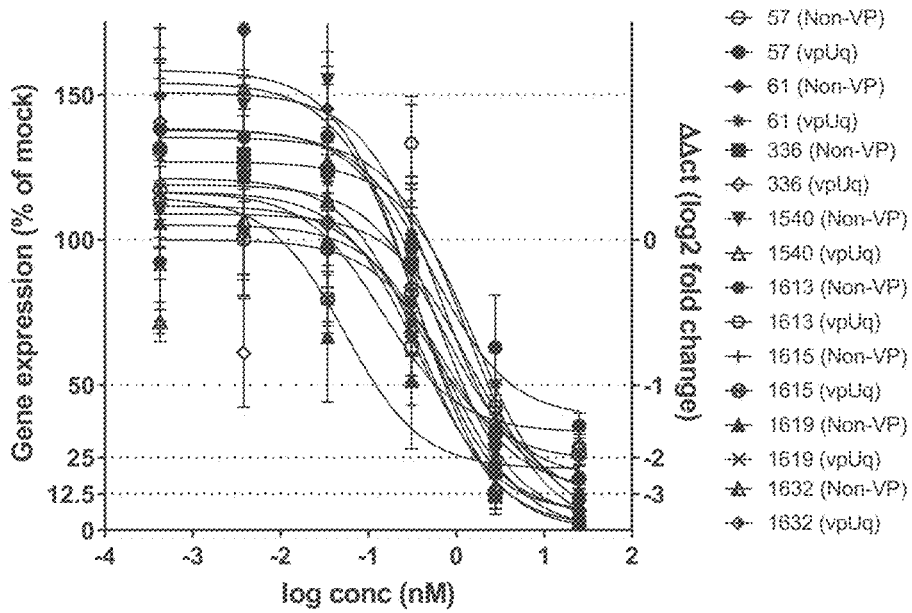


FIG. 18A

In Vitro Activities of DUX4-AOCs With DUX4-siRNA With Vinylphosphonate

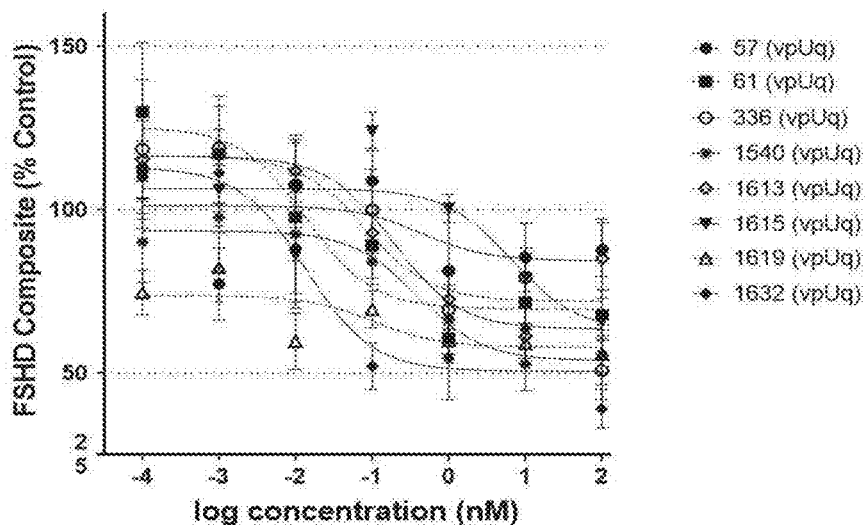
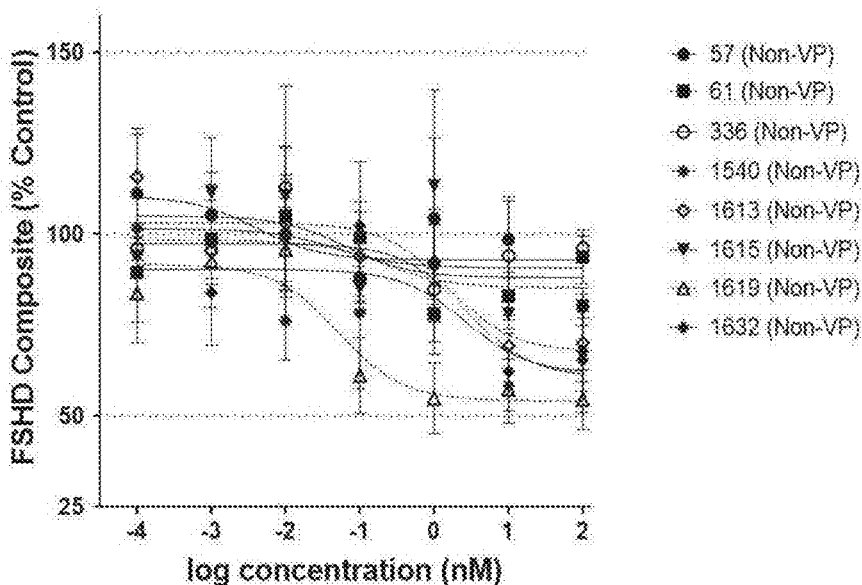


FIG. 18B

In Vitro Activities of DUX4-AOCs with DUX4-siRNA Without Vinylphosphonate



In Vivo Reduction of Nuclear Localized Lnc-RNA Malat1 in Skeletal Muscle
in Mice by siMalat1-AOC

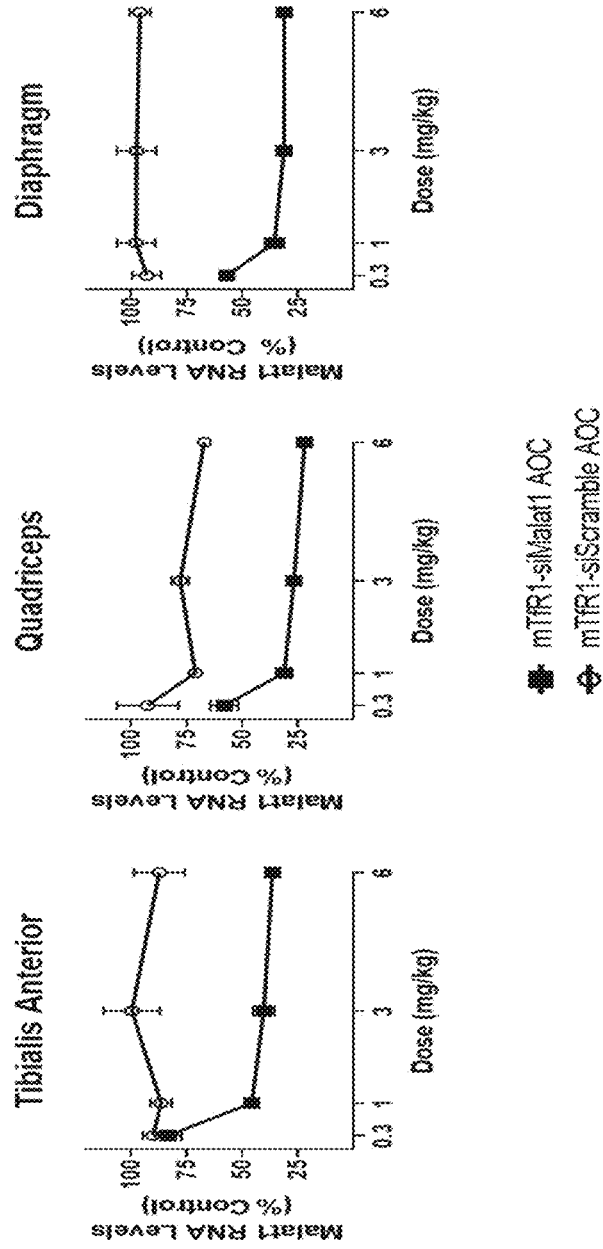
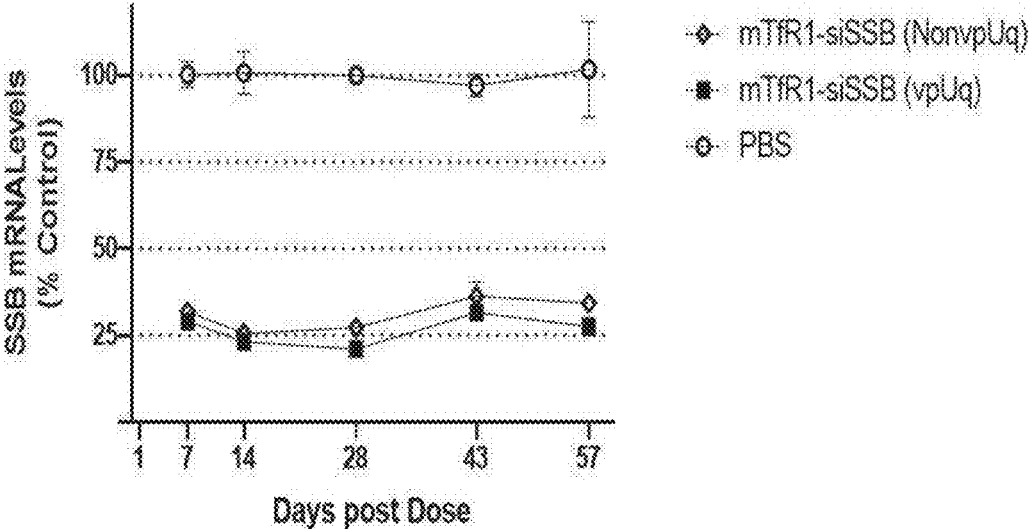


FIG. 19

FIG. 20

In Vivo Reduction of SSB mRNA in Skeletal Muscle in Mice by siSSB-AOCs



COMPOSITIONS AND METHODS OF TREATING FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Application Ser. No. 17/200,612, filed on Mar. 12, 2021, which claims the benefit of U.S. Provisional Application No. 62/992,071 filed on Mar. 19, 2020, and U.S. Provisional Application No. 63/066,655 filed on Aug. 17, 2020, each of which is incorporated herein by reference in its entirety.

REFERENCE TO A SEQUENCE LISTING XML

[0002] This application contains a Sequence Listing which has been submitted electronically in XML format. The Sequence Listing XML is incorporated herein by reference. Said XML file, created on Nov. 17, 2022, is named 45532-742_301_SL.xml and is 1,928,393 bytes in size.

BACKGROUND OF THE DISCLOSURE

[0003] Gene suppression by RNA-induced gene silencing provides several levels of control: transcription inactivation, small interfering RNA (siRNA)-induced mRNA degradation, and siRNA-induced transcriptional attenuation. In some instances, RNA interference (RNAi) provides long lasting effect over multiple cell divisions. As such, RNAi represents a viable method useful for drug target validation, gene function analysis, pathway analysis, and disease therapeutics.

INCORPORATION BY REFERENCE

[0004] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

SUMMARY OF THE DISCLOSURE

[0005] Disclosed herein, in certain embodiments, are polynucleic acid molecules and pharmaceutical compositions for modulating a gene associated with muscle atrophy, especially Facioscapulohumeral muscular dystrophy (FSHD). In some embodiments, also described herein are methods of treating muscle atrophy, especially FSHD, with a polynucleic acid molecule or a polynucleic acid molecule conjugate disclosed herein.

[0006] Disclosed herein, in certain embodiments, is a polynucleic acid molecule conjugate comprising an antibody or antigen binding fragment thereof conjugated to a polynucleic acid molecule that hybridizes to a target sequence of DUX4, and the polynucleic acid molecule conjugate mediates RNA interference against the DUX4. In certain embodiments, the antibody or antigen binding fragment thereof comprises a non-human antibody or binding fragment thereof, a human antibody or antigen binding fragment thereof, a humanized antibody or antigen binding fragment thereof, chimeric antibody or antigen binding fragment thereof, monoclonal antibody or antigen binding fragment thereof, divalent Fab', divalent Fab2, single-chain variable fragment (scFv), diabody, minibody, nanobody, single-domain antibody (sdAb), or camelid antibody or antigen binding fragment thereof. In certain embodi-

ments, the antibody or antigen binding fragment thereof is an anti-transferrin receptor antibody or antigen binding fragment thereof.

[0007] In certain embodiments, the polynucleic acid molecule comprises a sense strand and/or an antisense strand, and wherein the sense strand and/or the antisense strand each independently comprises at least one 2' modified nucleotide, at least one modified internucleotide linkage, or at least one inverted abasic moiety. In certain embodiments, the polynucleotide hybridizes to at least 8 contiguous bases of the target sequence of DUX4. In certain embodiments, the polynucleotide is from about 8 to about 50 nucleotides in length or from about 10 to about 30 nucleotides in length. In certain embodiments, the polynucleic acid molecule comprises a sense strand and/or an antisense strand, and the sense strand comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a sequence selected from SEQ ID NOs: 1-70 or SEQ ID NOs: 141-210. Alternatively and/or additionally, the polynucleic acid molecule comprises a sense strand and/or an antisense strand, and the antisense strand comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a sequence selected from SEQ ID NOs: 71-140 or SEQ ID NOs: 211-280.

[0008] In certain embodiments, the polynucleotide comprises at least one 2' modified nucleotide, and further the 2' modified nucleotide comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified nucleotide, or comprises locked nucleic acid (LNA) or ethylene nucleic acid (ENA), or comprises a combination thereof. In certain embodiments, the at least one modified internucleotide linkage comprises a phosphorothioate linkage or a phosphorodithioate linkage. In certain embodiments, the polynucleic acid molecule comprises 3 or more 2' modified nucleotides selected from 2'-O-methyl and 2'-deoxy-2'-fluoro. In certain embodiments, the polynucleic acid molecule comprises a 5'-terminal vinylphosphonate modified nucleotide, such as those described in U.S. Publication No. 2019/0192681.

[0009] In certain embodiments, the 2' modified nucleotide is 2'-O-methyl modified nucleotide, and 2'-O-methyl modified nucleotide is at the 5'-end of the sense strand and/or the antisense strand. In some embodiments, the 2'-O-methyl modified nucleotide is a purine nucleotide, or the 2'-O-methyl modified nucleotide is a pyridine nucleotide. In certain embodiments, the sense and/or antisense strands comprise at least two, three, four consecutive the 2'-O-methyl modified nucleotides at the 5'-end.

[0010] In certain embodiments, the polynucleic acid molecule conjugate comprises a linker connecting the target cell binding moiety to the polynucleic acid moiety. In such embodiments, the linker is C1-C6 alkyl linker, or the linker is a homobifunctional linker or heterobifunctional linker, and comprises a maleimide group, a dipeptide moiety, a benzoic acid group, or its derivative thereof. Alternatively and/or additionally, the linker is a cleavable or non-cleavable linker. In certain embodiments, a ratio between the polynucleic acid moiety and the target cell binding moiety is about 1:1, 2:1, 3:1, or 4:1.

[0011] In certain embodiments, the polynucleic acid moiety mediates RNA interference against the human DUX4 and modulates symptoms of muscle dystrophy in a subject. In some embodiments, the RNA interference comprises reducing expression of the mRNA transcript of DUX4 gene at least 50%, at least 60%, or at least 70% or more compared to a quantity of the mRNA transcript of DUX4 gene in an untreated cell. Alternatively and/or additionally, the RNA interference comprises affecting expression of a marker gene selected from a group comprising or consisting of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX in a cell. In some embodiments, the affecting expression of the marker gene is reducing expression of the marker gene at least 20%, at least 30%, at least 40%, at least 50%, at least 60% or more. In some embodiments, the muscle dystrophy is Facioscapulohumeral muscular dystrophy (FSHD).

[0012] In certain embodiments, polynucleic acid molecule conjugate comprises a molecule of Formula (I): A-X-B, where A is the antibody or antigen binding fragment thereof. B is the polynucleic acid molecule that hybridizes to a target sequence of DUX4, X is a bond or a non-polymeric linker, which is conjugated to a cysteine residue of A.

[0013] Disclosed herein, in certain embodiments, is a pharmaceutical composition comprising a polynucleic acid molecule conjugate as described herein, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated as a nanoparticle formulation. In some embodiments, the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, or intravenous, subcutaneous, or intrathecal administration.

[0014] The symptoms of FSHD include affects on skeletal muscles. The skeletal muscles affected by FSHD include muscles around the eyes and mouth, muscle of the shoulders, muscle of the upper arms, muscle of the lower legs, abdominal muscles and hip muscles. In some instances, the symptoms of FSHD also affects vision and hearing. In some instances, the symptoms of FSHD also affect the function of the heart or lungs. In some instances, the symptoms of FSHD include muscle weakness, muscle atrophy, muscle dystrophy, pain inflammation, contractures, scoliosis, lordosis, hypoventilation, abnormalities of the retina, exposure to keratitis, mild hearing loss, and EMG abnormality. The term muscle atrophy as used herein refers to a wide range of muscle related effects of FSHD.

[0015] Disclosed herein, in certain embodiments, is a method for treating muscular dystrophy in a subject in need thereof by providing a polynucleic acid conjugate as described herein, and administering the polynucleic acid conjugate to the subject in need thereof to treat the muscular dystrophy. The polynucleic acid conjugate reduces a quantity of the mRNA transcript of human DUX4. In some embodiments, the polynucleic acid moiety mediates RNA interference against the human DUX4 modulates muscle atrophy in a subject. In certain embodiments, the RNA interference comprises affecting expression of a marker gene selected from a group comprising or consisting of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX in a cell affected by a muscle dystrophy. Preferably, the muscular dystrophy is Facioscapulohumeral muscular dystrophy (FSHD).

[0016] Disclosed herein, in certain embodiments, is a use of the polynucleic acid molecule conjugate or a pharmaceutical composition as described herein for treating in a subject

diagnosed with or suspected to have Facioscapulohumeral muscular dystrophy (FSHD). Also disclosed herein, in certain embodiments, is a use of the polynucleic acid molecule conjugate or the pharmaceutical composition as described herein for manufacturing a medicament for treating in a subject diagnosed with or suspected to have Facioscapulohumeral muscular dystrophy (FSHD).

[0017] Disclosed herein, in certain embodiments, is a kit comprising the polynucleic acid molecule conjugate or the pharmaceutical composition as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings below. The patent application file contains at least one drawing executed in color. Copies of this patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0019] FIG. 1 illustrates a diagram of FSHD pathology.

[0020] FIG. 2 shows a flowchart diagram of in silico selection of DUX4 siRNA.

[0021] FIG. 3 illustrates the location and numbers of selected DUX4 siRNA in the DUX4 mRNA transcript.

[0022] FIG. 4 shows immunofluorescent detection of DUX4 expression in myonuclei.

[0023] FIG. 5 shows bar graphs of siRNA-mediated reduction of DUX4-target biomarker gene expressions.

[0024] FIGS. 6A-B show graphs of the siRNA-mediated reduction of DUX4-target biomarker gene expressions in cultured FSHD primary myotubes and a FSHD composite of the siRNA-mediated reduction of DUX4-target biomarker gene expressions in cultured FSHD primary myotubes

[0025] FIG. 7 shows a bar graph of ACTA1 gene expression in myotubes with treatment of DUX4 siRNA at a concentration of 10 nM.

[0026] FIG. 8 shows FSHD composite expression in myotubes with treatment of DUX4 siRNA at a concentration of 10 nM.

[0027] FIG. 9 shows FSHD composite expression in myotubes with treatment of DUX4 siRNA at a concentration of 0.5 nM.

[0028] FIG. 10 shows a flowchart diagram of the selection of DUX4 top 28 siRNAs based on data from initial screening.

[0029] FIGS. 11A-B show FSHD composite expression in two FSHD primary myotubes upon treatment with DUX4 siRNAs at a concentration of 10 nM and 0.5 nM.

[0030] FIG. 12 shows a KD correlation analysis identifying DUX4 siRNA effective in one or more FSHD primary myotubes.

[0031] FIG. 13 shows ACTA1 gene expression in patient-derived myotubes with treatment of DUX4 siRNA at a concentration of 10 nM.

[0032] FIG. 14 shows FSHD composite expression in patient-derived myotubes with treatment of DUX4 siRNA at a concentration of 10 nM.

[0033] FIG. 15 shows FSHD composite expression in 6 patient-derived myotubes with treatment of DUX4 siRNA.

[0034] FIGS. 16A-C show graphs of FSHD composite expression in 3 patient-derived myotubes with treatment of 14 selected DUX4 siRNAs.

[0035] FIGS. 17 A-C show graphs of FSHD composite expression in 3 FSHD patient-derived myotubes with treatment of 8 selected DUX4 siRNAs.

[0036] FIGS. 18 A-B show graphs of FSHD composite expression in cultured FSHD primary myotubes with treatment of 8 antibody DUX4-siRNA conjugates (DUX4-AOCs) without vinylphosphonate or 8 antibody DUX4-siRNA conjugates with vinylphosphonate.

[0037] FIG. 19 shows graphs of the AOC-mediated in vivo reduction of nuclear localized lnc-RNA Malat1 levels in skeletal muscles in mice.

[0038] FIG. 20 shows a graph of the sustained SSB-AOC-mediated in vivo reduction of SSB mRNA levels in murine skeletal muscles with a single dose of 3 mg/kg siRNA during an 8-week period.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0039] Muscle atrophy is the loss of muscle mass or the progressive weakening and degeneration of muscles, such as skeletal or voluntary muscles that controls movement, cardiac muscles, and smooth muscles. Various pathophysiological conditions including disuse, starvation, cancer, diabetes, and renal failure, or treatment with glucocorticoids result in muscle atrophy and loss of strength. The phenotypical effects of muscle atrophy are induced by various molecular events, including inhibition of muscle protein synthesis, enhanced turnover of muscle proteins, abnormal regulation of satellite cells differentiation, and abnormal conversion of muscle fibers types.

[0040] FSHD is a rare, progressive and disabling disease for which there are no approved treatments. FSHD is one of the most common forms of muscular dystrophy and affects both sexes equally, with onset typically in teens and young adults. FSHD is characterized by progressive skeletal muscle loss that initially causes weakness in muscles in the face, shoulders, arms and trunk and progresses to weakness in muscles in lower extremities and the pelvic girdle. Skeletal muscle weakness results in significant physical limitations, including progressive loss of facial muscles that can cause an inability to smile or communicate, difficulty using arms for activities of daily living and difficulty getting out of bed, with many patients ultimately becoming dependent upon the use of a wheelchair for daily mobility activities. The majority of patients with FSHD also report experiencing chronic pain, anxiety and depression.

[0041] FSHD is caused by aberrant expression of a gene, DUX4, in skeletal muscle resulting in the inappropriate presence of DUX4 protein. DUX4 itself is a transcription factor that induces the expression of other genes and it is these inappropriately expressed downstream genes that result in the muscle pathology. Normally DUX4-driven gene expression is limited to germline and early stem cell development. In patients with FSHD, the DUX4 protein in skeletal muscle regulates other gene products, some of which are toxic to the muscle. Evidence of aberrant DUX4-driven gene expression is the major molecular signature that distinguishes muscle tissue affected by FSHD from healthy muscle. The result of aberrant DUX4 expression in FSHD is death of muscle and its replacement by fat, resulting in skeletal muscle weakness and progressive disability. Data

suggest that reducing expression of the DUX4 gene and its downstream transcriptional program could provide a disease-modifying therapeutic approach for the treatment of FSHD at its root cause.

[0042] There are two ways the DUX4 gene can be unsilenced, or de-repressed. In FSHD1, which comprises approximately 95% of FSHD patients, there are mutations that lead to the shortening of an array of DNA in a region near the end of the long arm of chromosome 4, known as D4Z4, which has repeats in the subtelomeric region of the chromosome. The D4Z4 region is abnormally shortened and contains between 1-10 repeats instead of the normal 11 to 100 repeats. This contraction causes hypomethylation of the D4Z4 region and de-repression of DUX4. Patients with FSHD2 do not have a meaningful D4Z4 repeat contraction, but have mutations in a regulatory gene, known as the SMCHD1 gene, that normally contributes to the repression of the DUX4 gene via DNA methylation. When that repression is lost due to the mutations of the SMCHD1 gene leading to the hypomethylation of the D4Z4 region, DUX4 is inappropriately expressed, inducing the disease state. FIG. 1 shows an illustrative diagram of FSHD pathology.

[0043] Nucleic acid (e.g., RNAi) therapy is a targeted therapy with high selectivity and specificity. However, in some instances, nucleic acid therapy is also hindered by poor intracellular uptake, limited blood stability and non-specific immune stimulation. To address these issues, various modifications of the nucleic acid composition are explored, such as for example, novel linkers for better stabilizing and/or lower toxicity, optimization of binding moiety for increased target specificity and/or target delivery, and nucleic acid polymer modifications for increased stability and/or reduced off-target effect.

[0044] In some embodiments, the arrangement or order of the different components that make-up the nucleic acid composition further effects intracellular uptake, stability, toxicity, efficacy, and/or non-specific immune stimulation. For example, if the nucleic acid component includes a binding moiety, a polymer, and a polynucleic acid molecule (or polynucleotide), the order or arrangement of the binding moiety, the polymer, and/or the polynucleic acid molecule (or polynucleotide) (e.g., binding moiety-polynucleic acid molecule-polymer, binding moiety-polymer-polynucleic acid molecule, or polymer-binding moiety-polynucleic acid molecule) further effects intracellular uptake, stability, toxicity, efficacy, and/or non-specific immune stimulation.

[0045] In some embodiments, described herein include polynucleic acid molecules and polynucleic acid molecule conjugates for the treatment of Facioscapulohumeral Muscular Dystrophy (FSHD) especially muscle dystrophy and/or muscle atrophy associated therewith. In some instances, the polynucleic acid molecule conjugates described herein enhance intracellular uptake, stability, and/or efficacy. In some cases, the polynucleic acid molecule conjugates comprise an antibody or antigen binding fragment thereof conjugated to a polynucleic acid molecule. In some cases, the polynucleic acid molecules that hybridize to target sequences of DUX4, preferably human DUX4.

[0046] Additional embodiments described herein include methods of treating FSHD, comprising administering to a subject a polynucleic acid molecule or a polynucleic acid molecule conjugate described herein.

Polynucleic Acid Molecules

[0047] In certain embodiments, a polynucleic acid molecule hybridizes to a target sequence of Double homeobox 4 (DUX4) gene. In some instances, a polynucleic acid molecule described herein hybridizes to a target sequence of human DUX4 gene (DUX4) and reduces DUX4 mRNA in muscle cells.

[0048] In some embodiments, the polynucleic acid molecule comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 1-70. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 141-210. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 71-140. In some embodiments, the polynucleic acid molecule comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 211-280.

[0049] In some embodiments, the polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide. In some instances, the first polynucleotide comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 1-70. In some cases, the second polynucleotide comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 71-140. In some cases, the polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide. In some instances, the first polynucleotide comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 141-210. In some cases, the second polynucleotide comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 211-280.

[0050] In some embodiments, the polynucleic acid molecule comprises a sense strand (e.g., a passenger strand) and an antisense strand (e.g., a guide strand). In some instances, the sense strand (e.g., the passenger strand) comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 1-70. In some instances, the antisense strand (e.g., the guide strand) comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 71-140. In some embodiments, the polynucleic acid molecule comprises a sense strand (e.g., a passenger strand) and an antisense strand (e.g., a guide strand). In some instances, the sense strand (e.g., the passenger strand) comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence

selected from SEQ ID NOs: 141-210. In some instances, the antisense strand (e.g., the guide strand) comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 211-280.

[0051] In some instances, the sense strand comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 1, 2, 3, 6, 14, 36, 52, 56, 61, 62, 63, 65, 66. In some instances, the antisense strand comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from 71, 72, 73, 76, 84, 106, 122, 127, 131, 132, 133, 135, 136. In some instances, the siRNA comprises sense strand and antisense strand as presented in Table 11.

[0052] In some instances, the sense strand comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 141, 142, 143, 146, 176, 192, 196, 201, 202, 203, 205, 206. In some instances, the antisense strand comprises a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a sequence selected from SEQ ID NOs: 211, 212, 213, 216, 246, 262, 266, 271, 272, 273, 275, 276. In some instances, the siRNA comprises sense strand and antisense strand as presented in Table 12.

[0053] In some embodiments, the polynucleic acid molecule described herein comprises RNA or DNA. In some cases, the polynucleic acid molecule comprises RNA. In some instances, RNA comprises short interfering RNA (siRNA), short hairpin RNA (shRNA), microRNA (miRNA), double-stranded RNA (dsRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), or heterogeneous nuclear RNA (hnRNA). In some instances, RNA comprises shRNA. In some instances, RNA comprises miRNA. In some instances, RNA comprises dsRNA. In some instances, RNA comprises tRNA. In some instances, RNA comprises rRNA. In some instances, RNA comprises hnRNA. In some instances, the oligonucleotide is a phosphorodiamidate morpholino oligomers (PMO), which are short single-stranded oligonucleotide analogs that are built upon a backbone of morpholine rings connected by phosphorodiamidate linkages. In some instances, the RNA comprises siRNA. In some instances, the polynucleic acid molecule comprises siRNA.

[0054] In some embodiments, the polynucleic acid molecule is from about 8 to about 50 nucleotides in length. In some embodiments, the polynucleic acid molecule is from about 10 to about 50 nucleotides in length. In some instances, the polynucleic acid molecule is from about 10 to about 30, from about 15 to about 30, from about 18 to about 25, from about 18 to about 24, from about 19 to about 23, or from about 20 to about 22 nucleotides in length.

[0055] In some embodiments, the polynucleic acid molecule is about 50 nucleotides in length. In some instances, the polynucleic acid molecule is about 45 nucleotides in length. In some instances, the polynucleic acid molecule is about 40 nucleotides in length. In some instances, the polynucleic acid molecule is about 35 nucleotides in length. In some instances, the polynucleic acid molecule is about 30 nucleotides in length. In some instances, the polynucleic

in length. In some instances, the second polynucleotide is about 11 nucleotides in length. In some instances, the second polynucleotide is about 10 nucleotides in length. In some instances, the second polynucleotide is about 8 nucleotides in length. In some instances, the second polynucleotide is between about 8 and about 50 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 50 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 45 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 40 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 35 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 30 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 25 nucleotides in length. In some instances, the second polynucleotide is between about 10 and about 20 nucleotides in length. In some instances, the second polynucleotide is between about 15 and about 25 nucleotides in length. In some instances, the second polynucleotide is between about 15 and about 30 nucleotides in length. In some instances, the second polynucleotide is between about 12 and about 30 nucleotides in length.

[0061] In some embodiments, the polynucleic acid molecule comprises a first polynucleotide and a second polynucleotide. In some instances, the polynucleic acid molecule further comprises a blunt terminus, an overhang, or a combination thereof. In some instances, the blunt terminus is a 5' blunt terminus, a 3' blunt terminus, or both. In some cases, the overhang is a 5' overhang, 3' overhang, or both. In some cases, the overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-base pairing nucleotides. In some cases, the overhang comprises 1, 2, 3, 4, 5, or 6 non-base pairing nucleotides. In some cases, the overhang comprises 1, 2, 3, or 4 non-base pairing nucleotides. In some cases, the overhang comprises 1 non-base pairing nucleotide. In some cases, the overhang comprises 2 non-base pairing nucleotides. In some cases, the overhang comprises 3 non-base pairing nucleotides. In some cases, the overhang comprises 4 non-base pairing nucleotides. In some embodiments, the polynucleic acid molecule comprises a sense strand and an antisense strand, and the antisense strand includes two non-base pairing nucleotides as an overhang at the 3'-end while the sense strand has no overhang. Optionally, in such embodiments, the non-base pairing nucleotides have a sequence of TT, dTdT, or UU. In some embodiments, the polynucleic acid molecule comprises a sense strand and an antisense strand, and the sense strand has one or more nucleotides at the 5'-end that are complementary to the antisense sequence.

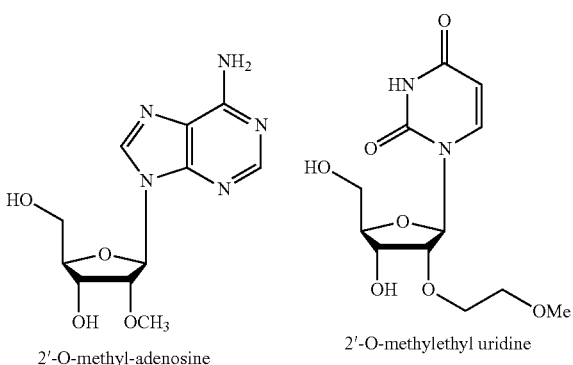
[0062] In some embodiments, the sequence of the polynucleic acid molecule is at least 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 99.5% complementary to a target sequence of DUX4. In some embodiments, the target sequence of DUX4 is a nucleic acid sequence of about 10-50 base pair length, about 15-50 base pair length, 15-40 base pair length, 15-30 base pair length, or 15-25 base pair length sequences in DUX4, in which the first nucleotide of the target sequence starts at any nucleotide in DUX4 mRNA transcript in the coding region, or in the 5' or 3'-untranslated region (UTR). For example, the first nucleotide of the target sequence can be selected so that it starts at the nucleic acid location (nal, number starting from

the 5'-end of the full length of DUX mRNA, e.g., the 5-end first nucleotide is nal. 1) 1, nal 2, nal 3, nal 4, nal 5, nal 6, nal 7, nal 8, nal 9, nal 10, nal 11, nal 12, nal 13, nal 14, nal 15, nal 16, nal 17, or any other nucleic acid location in the coding or noncoding regions (5' or 3'-untranslated region) of DUX mRNA. In some embodiments, the first nucleotide of the target sequence can be selected so that it starts at a location within, or between, nal 10-nal 15, nal 10-nal 20, nal 50-nal 60, nal 55-nal 65, nal 75-nal 85, nal 95-nal 105, nal 135-nal 145, nal 155-nal 165, nal 225-nal 235, nal 265-nal 275, nal 275-nal 285, nal 285-nal 295, nal 325-nal 335, nal 335-nal 345, nal 385-nal 395, nal 515-nal 525, nal 665-nal 675, nal 675-nal 685, nal 695-nal 705, nal 705-nal 715, nal 875-nal 885, nal 885-nal 895, nal 895-nal 905, nal 1035-nal 1045, nal 1045-nal 1055, nal 1125-nal 1135, nal 1135-nal 1145, nal 1145-nal 1155, nal 1155-nal 1165, nal 1125-nal 1135, nal 1155-nal 1165, nal 1225-nal 1235, nal 1235-nal 1245, nal 1275-nal 1285, nal 1285-nal 1295, nal 1305-nal 1315, nal 1125-nal 1135, nal 1155-nal 1165, nal 1225-nal 1235, nal 1235-nal 1245, nal 1275-nal 1285, nal 1285-nal 1295, nal 1305-nal 1315, nal 1315-nal 1325, nal 1335-nal 1345, nal 1345-nal 1355, nal 1525-nal 1535, nal 1535-nal 1545, nal 1605-nal 1615, nal 1615-c. 1625, nal 1625-nal 1635.

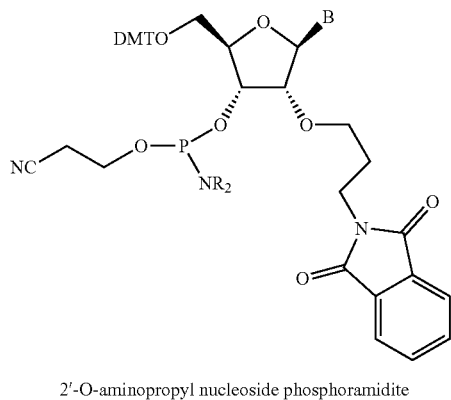
[0063] In some embodiments, the sequence of the polynucleic acid molecule is at least 50% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 60% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 70% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 80% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 90% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 95% complementary to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule is at least 99% complementary to a target sequence described herein. In some instances, the sequence of the polynucleic acid molecule is 100% complementary to a target sequence described herein.

[0064] In some embodiments, the sequence of the polynucleic acid molecule has 5 or less mismatches to a target sequence described herein. In some embodiments, the sequence of the polynucleic acid molecule has 4 or less mismatches to a target sequence described herein. In some instances, the sequence of the polynucleic acid molecule has 3 or less mismatches to a target sequence described herein. In some cases, the sequence of the polynucleic acid molecule has 2 or less mismatches to a target sequence described herein. In some cases, the sequence of the polynucleic acid molecule has 1 or less mismatches to a target sequence described herein.

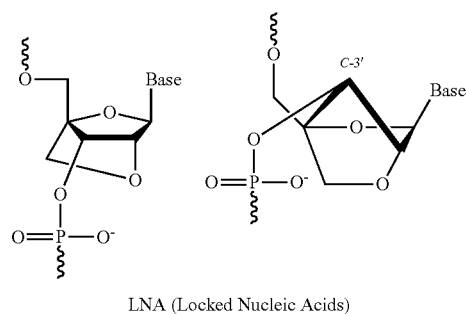
[0065] In some embodiments, a group of polynucleic acid molecules among all the polynucleic acid molecules potentially binds to the target sequence of DUX4 are selected to generate a polynucleic acid molecule library. In certain embodiments, such selection process is conducted in silico via one or more steps of eliminating less desirable polynucleic acid molecules from candidates. For example, in some embodiments, the selection process comprises an elimination step of one or more polynucleic acid molecule



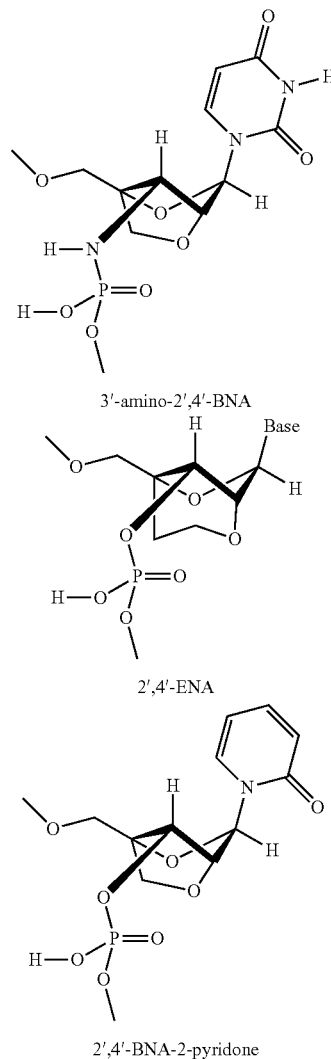
[0072] In some instances, the modification at the 2' hydroxyl group is a 2'-O-aminopropyl modification in which an extended amine group comprising a propyl linker binds the amine group to the 2' oxygen. In some instances, this modification neutralizes the phosphate derived overall negative charge of the oligonucleotide molecule by introducing one positive charge from the amine group per sugar and thereby improves cellular uptake properties due to its zwitterionic properties. An exemplary chemical structure of a 2'-O-aminopropyl nucleoside phosphoramidite is illustrated below.

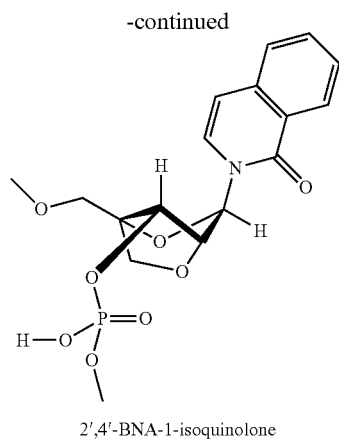


[0073] In some instances, the modification at the 2' hydroxyl group is a locked or bridged ribose modification (e.g., locked nucleic acid or LNA) in which the oxygen molecule bound at the 2' carbon is linked to the 4' carbon by a methylene group, thus forming a 2'-C,4'-C-oxy-methylene-linked bicyclic ribonucleotide monomer. Exemplary representations of the chemical structure of LNA are illustrated below. The representation shown to the left highlights the chemical connectivities of an LNA monomer. The representation shown to the right highlights the locked 3'-endo (³E) conformation of the furanose ring of an LNA monomer.



[0074] In some instances, the modification at the 2' hydroxyl group comprises ethylene nucleic acids (ENA) such as for example 2'-4'-ethylene-bridged nucleic acid, which locks the sugar conformation into a C_{3'}-endo sugar puckering conformation. ENA are part of the bridged nucleic acids class of modified nucleic acids that also comprises LNA. Exemplary chemical structures of the ENA and bridged nucleic acids are illustrated below.



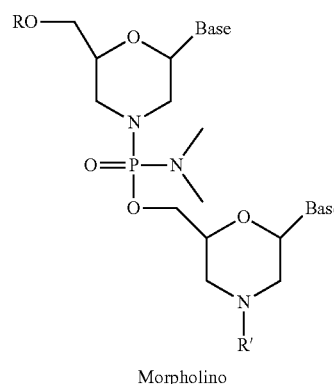


[0075] In some embodiments, additional modifications at the 2' hydroxyl group include 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA).

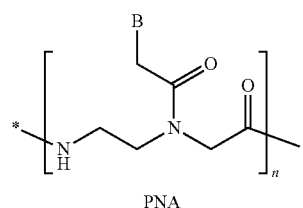
[0076] In some embodiments, nucleotide analogues comprise modified bases such as, but not limited to, 5-propynyluridine, 5-propynylcytidine, 6-methyladenine, 6-methylguanine, N, N-dimethyladenine, 2-propyladenine, 2-propylguanine, 2-aminoadenine, 1-methylinosine, 3-methyluridine, 5-methylcytidine, 5-methyluridine and other nucleotides having a modification at the 5 position, 5-(2-amino) propyl uridine, 5-halocytidine, 5-halouridine, 4-acetylcytidine, 1-methyladenosine, 2-methyladenosine, 3-methylcytidine, 6-methyluridine, 2-methylguanosine, 7-methylguanosine, 2, 2-dimethylguanosine, 5-methylaminoethyluridine, 5-methyloxuridine, deazanucleotides such as 7-deaza-adenosine, 6-azouridine, 6-azocytidine, 6-azothymidine, 5-methyl-2-thiouridine, other thio bases such as 2-thiouridine and 4-thiouridine and 2-thiocytidine, dihydrouridine, pseudouridine, queuosine, archaeosine, naphthyl and substituted naphthyl groups, any O- and N-alkylated purines and pyrimidines such as N6-methyladenosine, 5-methylcarbonylmethyluridine, uridine 5-oxyacetic acid, pyridine-4-one, pyridine-2-one, phenyl and modified phenyl groups such as aminophenol or 2,4, 6-trimethoxy benzene, modified cytosines that act as G-clamp nucleotides, 8-substituted adenines and guanines, 5-substituted uracils and thymines, azapyrimidines, carboxyhydroxyalkyl nucleotides, carboxyalkylaminoalkyl nucleotides, and alkylcarbonylalkylated nucleotides. Modified nucleotides also include those nucleotides that are modified with respect to the sugar moiety, as well as nucleotides having sugars or analogs thereof that are not ribosyl. For example, the sugar moieties, in some cases are or be based on, mannoses, arabinoses, glucopyranoses, galactopyranoses, 4'-thioribose, and other sugars, heterocycles, or carbocycles. The term nucleotide also includes what are known in the art as universal bases. By way of example, universal bases include but are not limited to 3-nitropyrrole, 5-nitroindole, or nebularine.

[0077] In some embodiments, nucleotide analogues further comprise morpholinos, peptide nucleic acids (PNAs), methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, 1', 5'-anhydrohexitol nucleic acids (HNAs), or a combination thereof.

Morpholino or phosphordiamidate morpholino oligo (PMO) comprises synthetic molecules whose structure mimics natural nucleic acid structure by deviates from the normal sugar and phosphate structures. In some instances, the five member ribose ring is substituted with a six member morpholino ring containing four carbons, one nitrogen and one oxygen. In some cases, the ribose monomers are linked by a phosphordiamidate group instead of a phosphate group. In such cases, the backbone alterations remove all positive and negative charges making morpholinos neutral molecules capable of crossing cellular membranes without the aid of cellular delivery agents such as those used by charged oligonucleotides.

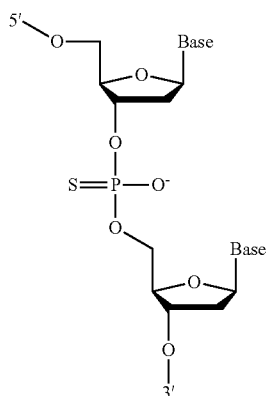


[0078] In some embodiments, peptide nucleic acid (PNA) does not contain sugar ring or phosphate linkage and the bases are attached and appropriately spaced by oligoglycine-like molecules, therefore, eliminating a backbone charge.

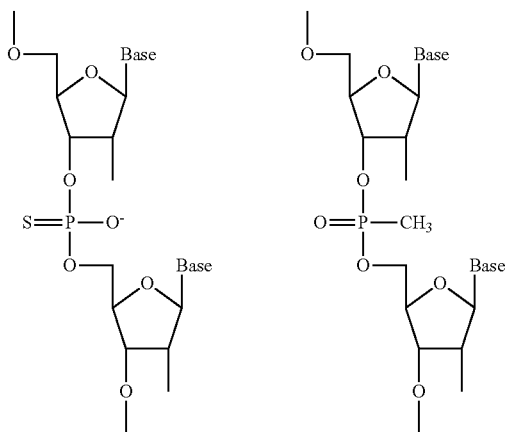


[0079] In some embodiments, one or more modifications optionally occur at the internucleotide linkage. In some instances, modified internucleotide linkage include, but is not limited to, phosphorothioates, phosphorodithioates, methylphosphonates, 5'-alkylenephosphonates, 5'-methylphosphonate, 3'-alkylene phosphonates, borontrifluoridates, borano phosphate esters and selenophosphates of 3'-5' linkage or 2'-5' linkage, phosphotriesters, thionoalkylphosphotriesters, hydrogen phosphonate linkages, alkyl phosphonates, alkylphosphonothioates, arylphosphonothioates, phosphoroselenoates, phosphorodiselenoates, phosphinates, phosphoramidates, 3'-alkylphosphoramidates, aminoalkylphosphoramidates, thionophosphoramidates, phosphoropiperazidates, phosphoroanilothioates, phosphoroanilidates, ketones, sulfones, sulfonamides, carbonates, carbamates, methylenehydrazos, methylenedimethylhydrazos, formacetals, thioformacetals, oximes, methyleneimi-

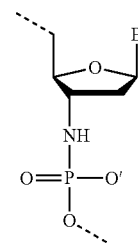
nos, methylenemethyliminos, thioamides, linkages with riboacetyl groups, aminoethyl glycine, silyl or siloxane linkages, alkyl or cycloalkyl linkages with or without heteroatoms of, for example, 1 to 10 carbons that are saturated or unsaturated and/or substituted and/or contain heteroatoms, linkages with morpholino structures, amides, polyamides wherein the bases are attached to the aza nitrogens of the backbone directly or indirectly, and combinations thereof. Phosphorothioate antisense oligonucleotides (PS ASO) are antisense oligonucleotides comprising a phosphorothioate linkage. An exemplary PS ASO is illustrated below.



[0080] In some instances, the modification is a methyl or thiol modification such as methylphosphonate or thiolphosphonate modification. Exemplary thiolphosphonate nucleotide (left) and methylphosphonate nucleotide (right) are illustrated below.

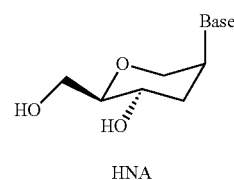


[0081] In some instances, a modified nucleotide includes, but is not limited to, 2'-fluoro N3-P5'-phosphoramidites illustrated as:



N3'-P5' Phosphoramidate

[0082] In some instances, a modified nucleotide includes, but is not limited to, hexitol nucleic acid (or 1', 5'-anhydrohexitol nucleic acids (HNA)) illustrated as:



[0083] In some embodiments, one or more modifications further optionally include modifications of the ribose moiety, phosphate backbone and the nucleoside, or modifications of the nucleotide analogues at the 3' or the 5' terminus. For example, the 3' terminus optionally include a 3' cationic group, or by inverting the nucleoside at the 3'-terminus with a 3'-3' linkage. In another alternative, the 3'-terminus is optionally conjugated with an aminoalkyl group, e.g. a 3' C5-aminoalkyl dT. In an additional alternative, the 3'-terminus is optionally conjugated with an abasic site, e.g., with an apurinic or apyrimidinic site. In some instances, the 5'-terminus is conjugated with an aminoalkyl group. e.g. a 5'-O-alkylamino substituent. In some cases, the 5'-terminus is conjugated with an abasic site. e.g., with an apurinic or apyrimidinic site.

[0084] In some embodiments, the polynucleic acid molecule comprises one or more of the artificial nucleotide analogues described herein. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of the artificial nucleotide analogues described herein. In some embodiments, the artificial nucleotide analogues include 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiolphosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, or a combination thereof. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of the artificial nucleotide analogues selected from 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-

methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiolphosphonate nucleotides, 2'-fluoro N3-P5-phosphoramidites, or a combination thereof. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of 2'-O-methyl modified nucleotides. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of 2'-O-methoxyethyl (2'-O-MOE) modified nucleotides. In some instances, the polynucleic acid molecule comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 25, or more of thiolphosphonate nucleotides.

[0085] In some instances, the polynucleic acid molecule comprises at least one of: from about 5% to about 100% modification, from about 10% to about 100% modification, from about 20% to about 100% modification, from about 30% to about 100% modification, from about 40% to about 100% modification, from about 50% to about 100% modification, from about 60% to about 100% modification, from about 70% to about 100% modification, from about 80% to about 100% modification, and from about 90% to about 100% modification.

[0086] In some cases, the polynucleic acid molecule comprises at least one of: from about 10% to about 90% modification, from about 20% to about 90% modification, from about 30% to about 90% modification, from about 40% to about 90% modification, from about 50% to about 90% modification, from about 60% to about 90% modification, from about 70% to about 90% modification, and from about 80% to about 100% modification.

[0087] In some cases, the polynucleic acid molecule comprises at least one of: from about 10% to about 80% modification, from about 20% to about 80% modification, from about 30% to about 80% modification, from about 40% to about 80% modification, from about 50% to about 80% modification, from about 60% to about 80% modification, and from about 70% to about 80% modification.

[0088] In some instances, the polynucleic acid molecule comprises at least one of: from about 10% to about 70% modification, from about 20% to about 70% modification, from about 30% to about 70% modification, from about 40% to about 70% modification, from about 50% to about 70% modification, and from about 60% to about 70% modification.

[0089] In some instances, the polynucleic acid molecule comprises at least one of: from about 10% to about 60% modification, from about 20% to about 60% modification, from about 30% to about 60% modification, from about 40% to about 60% modification, and from about 50% to about 60% modification.

[0090] In some cases, the polynucleic acid molecule comprises at least one of: from about 10% to about 50% modification, from about 20% to about 50% modification, from about 30% to about 50% modification, and from about 40% to about 50% modification.

[0091] In some cases, the polynucleic acid molecule comprises at least one of: from about 10% to about 40% modification, from about 20% to about 40% modification, and from about 30% to about 40% modification.

[0092] In some cases, the polynucleic acid molecule comprises at least one of: from about 10% to about 30% modification, and from about 20% to about 30% modification.

[0093] In some cases, the polynucleic acid molecule comprises from about 10% to about 20% modification.

[0094] In some cases, the polynucleic acid molecule comprises from about 15% to about 90%, from about 20% to about 80%, from about 30% to about 70%, or from about 40% to about 60% modifications.

[0095] In additional cases, the polynucleic acid molecule comprises at least about 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% modification.

[0096] In some embodiments, the polynucleic acid molecule comprises at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22 or more modifications.

[0097] In some instances, the polynucleic acid molecule comprises at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22 or more modified nucleotides.

[0098] In some instances, from about 5 to about 100% of the polynucleic acid molecule comprise the artificial nucleotide analogues described herein. In some instances, about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the polynucleic acid molecule comprise the artificial nucleotide analogues described herein. In some instances, about 5% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 10% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 15% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 20% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 25% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 30% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 35% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 40% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 45% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 50% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 55% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 60% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 65% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 70% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 75% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 80% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 85% of the polynucleic acid molecule

comprises the artificial nucleotide analogues described herein. In some instances, about 90% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 95% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 96% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 97% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 98% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 99% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some instances, about 100% of the polynucleic acid molecule comprises the artificial nucleotide analogues described herein. In some embodiments, the artificial nucleotide analogues include 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, or a combination thereof.

[0099] In some embodiments, the polynucleic acid molecule comprises from about 1 to about 25 modifications in which the modification comprises an artificial nucleotide analogues described herein. In some embodiments, the polynucleic acid molecule comprises about 1 modification in which the modification comprises an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 2 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 3 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 4 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 5 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 6 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 7 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 8 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 9 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 10 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 11 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the poly-

nucleic acid molecule comprises about 12 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 13 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 14 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 15 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 16 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 17 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 18 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 19 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 20 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 21 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 22 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 23 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 24 modifications in which the modifications comprise an artificial nucleotide analogue described herein. In some embodiments, the polynucleic acid molecule comprises about 25 modifications in which the modifications comprise an artificial nucleotide analogue described herein.

[0100] In some embodiments, a polynucleic acid molecule is assembled from two separate polynucleotides wherein one polynucleotide comprises the sense strand and the second polynucleotide comprises the antisense strand of the polynucleic acid molecule. In other embodiments, the sense strand is connected to the antisense strand via a linker molecule, which in some instances is a polynucleotide linker or a non-nucleotide linker.

[0101] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein pyrimidine nucleotides in the sense strand comprises 2'-O-methylpyrimidine nucleotides and purine nucleotides in the sense strand comprise 2'-deoxy purine nucleotides. In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein pyrimidine nucleotides present in the sense strand comprise 2'-deoxy-2'-fluoro pyrimidine nucleotides and wherein purine nucleotides present in the sense strand comprise 2'-deoxy purine nucleotides.

[0102] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein the pyrimidine nucleotides when present in said antisense strand

are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides when present in said antisense strand are 2'-O-methyl purine nucleotides.

[0103] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein the pyrimidine nucleotides when present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and wherein the purine nucleotides when present in said antisense strand comprise 2'-deoxy-purine nucleotides.

[0104] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and at least one of sense strand and antisense strands has a plurality of (e.g., two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, etc) 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides. In some embodiments, where at least two out of the a plurality of 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides are consecutive nucleotides. In some embodiments, where consecutive 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides are located at the 5'-end of the sense strand and/or the antisense strand. In some embodiments, where consecutive 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides are located at the 3'-end of the sense strand and/or the antisense strand. In some embodiments, the sense strand of polynucleic acid molecule includes at least four, at least five, at least six consecutive 2'-O-methyl modified nucleotides at its 5' end and/or 3' end, or both. Optionally, in such embodiments, the sense strand of polynucleic acid molecule includes at least one, at least two, at least three, at least four 2'-deoxy-2'-fluoro modified nucleotides at the 3' end of the at least four, at least five, at least six consecutive 2'-O-methyl modified nucleotides at the polynucleotides' 5' end, or at the 5' end of the at least four, at least five, at least six consecutive 2'-O-methyl modified nucleotides at polynucleotides' 3' end. Also optionally, such at least two, at least three, at least four 2'-deoxy-2'-fluoro modified nucleotides are consecutive nucleotides.

[0105] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and at least one of sense strand and antisense strands has 2'-O-methyl modified nucleotide located at the 5'-end of the sense strand and/or the antisense strand. In some embodiments, at least one of sense strand and antisense strands has 2'-O-methyl modified nucleotide located at the 3'-end of the sense strand and/or the antisense strand. In some embodiments, the 2'-O-methyl modified nucleotide located at the 5'-end of the sense strand and/or the antisense strand is a purine nucleotide. In some embodiments, the 2'-O-methyl modified nucleotide located at the 5'-end of the sense strand and/or the antisense strand is a pyridine nucleotide.

[0106] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and the antisense strand has two or more consecutive 2'-deoxy-2'-fluoro modified nucleotides at 5'-end. In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and the antisense strand has two or more consecutive 2'-O-methyl modified nucleotides at 3'-end. In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and the antisense strand has at least 2, 3, 4, 5, 6, or 7 consecutive 2'-O-methyl modified nucleotides.

[0107] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and the sense strand comprises a nucleic acid of

5'-nsnsnnnnNfNfNfnnnnnnsnsa-3' (lower case (n)=2'-O-Me (methyl), Nf=2'-F (fluoro); s=phosphorothioate backbone modification). In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and the antisense strand comprises a nucleic acid of 5'-UfsNfsnnnNfnnnnnnnNfnNfnnsusu-3' (lower case (n)=2'-O-Me (methyl), Nf=2'-F (fluoro); s=phosphorothioate backbone modification). In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, and the sense strand comprises a nucleic acid of 5'-nsnsnnnnNfNfNfnnnnnnsnsa-3' (lower case (n)=2'-O-Me (methyl), Nf=2'-F (fluoro); s=phosphorothioate backbone modification) and the antisense strand comprises a nucleic acid of 5'-UfsNfsnnnNfnnnnnnnNfnNfnnsusu-3' (lower case (n)=2'-O-Me (methyl), Nf=2'-F (fluoro); s=phosphorothioate backbone modification).

[0108] In some embodiments, a polynucleic acid molecule comprises a sense strand and antisense strand, wherein the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In other embodiments, the terminal cap moiety is an inverted deoxy abasic moiety.

[0109] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, wherein the antisense strand comprises a glyceryl modification at the 3' end of the antisense strand.

[0110] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and in which the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

[0111] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the sense strand comprises about 1 to about 25, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or

more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and in which the antisense strand comprises about 1 to about 25 or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or one or more (e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 25 or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

[0112] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand and/or antisense strand, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand. In some embodiments, the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

[0113] In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, in which the antisense strand comprises about 1 to about 25 or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and the antisense strand comprises about 1 to about 25 or more, for

example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In other embodiments, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

[0114] In some embodiments, a polynucleic acid molecule described herein is a chemically-modified short interfering nucleic acid molecule having about 1 to about 25, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more phosphorothioate internucleotide linkages in each strand of the polynucleic acid molecule. In some embodiments, a polynucleic acid molecule comprises a sense strand and an antisense strand, and the antisense strand comprises a phosphate backbone modification at the 3' end of the antisense strand. Alternatively and/or additionally, a polynucleic acid molecule comprises a sense strand and an antisense strand, and the sense strand comprises a phosphate backbone modification at the 5' end of the antisense strand. In some instances, the phosphate backbone modification is a phosphorothioate. In some embodiments, the sense or antisense strand has three consecutive nucleosides that are coupled via two phosphorothioate backbone.

[0115] In another embodiment, a polynucleic acid molecule described herein comprises 2'-5' internucleotide linkages. In some instances, the 2'-5' internucleotide linkage(s) is at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both sequence strands. In addition instances, the 2'-5' internucleotide linkage(s) is present at various other positions within one or both sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands of the polynucleic acid molecule comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the polynucleic acid molecule comprise a 2'-5' internucleotide linkage.

[0116] In some embodiments, a polynucleic acid molecule is a single stranded polynucleic acid molecule that mediates RNAi activity in a cell or reconstituted in vitro system, wherein the polynucleic acid molecule comprises a single stranded polynucleotide having complementarity to a target nucleic acid sequence, and wherein one or more pyrimidine nucleotides present in the polynucleic acid are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the polynucleic acid are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and a terminal cap modification, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the

antisense sequence, the polynucleic acid molecule optionally further comprising about 1 to about 4 (e.g., about 1, 2, 3, or 4) terminal 2'-deoxynucleotides at the 3'-end of the polynucleic acid molecule, wherein the terminal nucleotides further comprise one or more (e.g., 1, 2, 3, or 4) phosphorothioate internucleotide linkages, and wherein the polynucleic acid molecule optionally further comprises a terminal phosphate group, such as a 5'-terminal phosphate group.

[0117] In some cases, one or more of the artificial nucleotide analogues described herein are resistant toward nucleases such as for example ribonuclease such as RNase H, deoxyribonuclease such as DNase, or exonuclease such as 5'-3' exonuclease and 3'-5' exonuclease when compared to natural polynucleic acid molecules. In some instances, artificial nucleotide analogues comprising 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, 2'-fluoro N3-P5'-phosphoramidites, or combinations thereof are resistant toward nucleases such as for example ribonuclease such as RNase H, deoxyribonuclease such as DNase, or exonuclease such as 5'-3' exonuclease and 3'-5' exonuclease. In some instances, 2'-O-methyl modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-methoxyethyl (2'-O-MOE) modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-aminopropyl modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-deoxy modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-deoxy-2'-fluoro modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-aminopropyl (2'-O-AP) modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-dimethylaminoethyl (2'-O-DMAOE) modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-dimethylaminopropyl (2'-O-DMAP) modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, 2'-O-N-methylacetamido (2'-O-NMA) modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, LNA modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, ENA modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, HNA modified polynucleic acid molecule is nuclease resistance

(e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, morpholinos is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, PNA modified polynucleic acid molecule is resistant to nucleases (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, methylphosphonate nucleotides modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, thiophosphonate nucleotides modified polynucleic acid molecule is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, polynucleic acid molecule comprising 2'-fluoro N3-P5'-phosphoramidites is nuclease resistance (e.g., RNase H, DNase, 5'-3' exonuclease or 3'-5' exonuclease resistance). In some instances, the 5' conjugates described herein inhibit 5'-3' exonucleolytic cleavage. In some instances, the 3' conjugates described herein inhibit 3'-5' exonucleolytic cleavage.

[0118] In some embodiments, one or more of the artificial nucleotide analogues described herein have increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. The one or more of the artificial nucleotide analogues comprising 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, LNA, ENA, PNA, HNA, morpholino, methylphosphonate nucleotides, thiophosphonate nucleotides, or 2'-fluoro N3-P5'-phosphoramidites have increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-methyl modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-methoxyethyl (2'-O-MOE) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-aminopropyl (2'-O-AP) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-deoxy modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-deoxy-2'-fluoro modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-aminopropyl (2'-O-AP) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-dimethylaminoethyl (2'-O-DMAOE) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-dimethylaminopropyl (2'-O-DMAP) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-N-methylacetamido (2'-O-NMA) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule.

to an equivalent natural polynucleic acid molecule. In some instances, 2'-O-N-methylacetamido (2'-O-NMA) modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, LNA modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, ENA modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, PNA modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, HNA modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, morpholino modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, methylphosphonate nucleotides modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, thiolphosphonate nucleotides modified polynucleic acid molecule has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some instances, polynucleic acid molecule comprising 2'-fluoro N3-P5'-phosphoramidites has increased binding affinity toward their mRNA target relative to an equivalent natural polynucleic acid molecule. In some cases, the increased affinity is illustrated with a lower K_d, a higher melt temperature (T_m), or a combination thereof.

[0119] In some embodiments, a polynucleic acid molecule described herein is a chirally pure (or stereo pure) polynucleic acid molecule, or a polynucleic acid molecule comprising a single enantiomer. In some instances, the polynucleic acid molecule comprises L-nucleotide. In some instances, the polynucleic acid molecule comprises D-nucleotides. In some instance, a polynucleic acid molecule composition comprises less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1%, or less of its mirror enantiomer. In some cases, a polynucleic acid molecule composition comprises less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1%, or less of a racemic mixture. In some instances, the polynucleic acid molecule is a polynucleic acid molecule described in: U.S. Patent Publication Nos: 2014/194610 and 2015/211006; and PCT Publication No: WO2015107425.

[0120] In some embodiments, a polynucleic acid molecule described herein is further modified to include an aptamer conjugating moiety. In some instances, the aptamer conjugating moiety is a DNA aptamer conjugating moiety. In some instances, the aptamer conjugating moiety is Alphamer (Centauri Therapeutics), which comprises an aptamer portion that recognizes a specific cell-surface target and a portion that presents a specific epitopes for attaching to circulating antibodies. In some instance, a polynucleic acid molecule described herein is further modified to include an aptamer conjugating moiety as described in: U.S. Pat. Nos. 8,604,184, 8,591,910, and 7,850,975.

[0121] In additional embodiments, a polynucleic acid molecule described herein is modified to increase its stability. In some embodiment, the polynucleic acid molecule is RNA

(e.g., siRNA). In some instances, the polynucleic acid molecule is modified by one or more of the modifications described above to increase its stability. In some cases, the polynucleic acid molecule is modified at the 2' hydroxyl position, such as by 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modification or by a locked or bridged ribose conformation (e.g., LNA or ENA). In some cases, the polynucleic acid molecule is modified by 2'-O-methyl and/or 2'-O-methoxyethyl ribose. In some cases, the polynucleic acid molecule also includes morpholinos, PNAs, HNA, methylphosphonate nucleotides, thiolphosphonate nucleotides, and/or 2'-fluoro N3-P5'-phosphoramidites to increase its stability. In some instances, the polynucleic acid molecule is a chirally pure (or stereo pure) polynucleic acid molecule. In some instances, the chirally pure (or stereo pure) polynucleic acid molecule is modified to increase its stability. Suitable modifications to the RNA to increase stability for delivery will be apparent to the skilled person.

[0122] In some instances, the polynucleic acid molecule is a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. In some instances, the polynucleic acid molecule is assembled from two separate polynucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (e.g., each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 19, 20, 21, 22, 23, or more base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the polynucleic acid molecule is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the polynucleic acid molecule are linked by means of a nucleic acid based or non-nucleic acid-based linker(s).

[0123] In some cases, the polynucleic acid molecule is a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. In other cases, the polynucleic acid molecule is a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide

sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide is processed either in vivo or in vitro to generate an active polynucleic acid molecule capable of mediating RNAi. In additional cases, the polynucleic acid molecule also comprises a single-stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such polynucleic acid molecule does not require the presence within the polynucleic acid molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide further comprises a terminal phosphate group, such as a 5'-phosphate (see for example Martinez et al., 2002, *Cell.*, 110, 563-574 and Schwarz et al., 2002, *Molecular Cell.* 10, 537-568), or 5', 3'-diphosphate.

[0124] In some instances, an asymmetric hairpin is a linear polynucleic acid molecule comprising an antisense region, a loop portion that comprises nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complimentary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin polynucleic acid molecule comprises an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 nucleotides) and a loop region comprising about 4 to about 8 nucleotides, and a sense region having about 3 to about 18 nucleotides that are complementary to the antisense region. In some cases, the asymmetric hairpin polynucleic acid molecule also comprises a 5'-terminal phosphate group that is chemically modified. In additional cases, the loop portion of the asymmetric hairpin polynucleic acid molecule comprises nucleotides, non-nucleotides, linker molecules, or conjugate molecules.

[0125] In some embodiments, an asymmetric duplex is a polynucleic acid molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complimentary nucleotides to base pair with the antisense region and form a duplex. For example, an asymmetric duplex polynucleic acid molecule comprises an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g., about 19 to about 22 nucleotides) and a sense region having about 3 to about 18 nucleotides that are complementary to the antisense region.

[0126] In some cases, a universal base refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research.* 29, 2437-2447).

Polynucleic Acid Molecule Synthesis

[0127] In some embodiments, a polynucleic acid molecule described herein is constructed using chemical synthesis and/or enzymatic ligation reactions using procedures known in the art. For example, a polynucleic acid molecule is

chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the polynucleic acid molecule and target nucleic acids. Exemplary methods include those described in: U.S. Pat. Nos. 5,142,047; 5,185,444; 5,889,136; 6,008,400; and 6,111,086; PCT Publication No. WO2009099942; or European Publication NO. 1579015. Additional exemplary methods include those described in: Griffey et al., "2'-O-aminopropyl ribonucleotides: a zwitterionic modification that enhances the exonuclease resistance and biological activity of antisense oligonucleotides," *J. Med. Chem.* 39(26):5100-5109 (1997); Obika, et al. "Synthesis of 2'-O,4'-C-methyleneuridine and -cytidine. Novel bicyclic nucleosides having a fixed C3, -endo sugar puckering". *Tetrahedron Letters* 38 (50): 8735 (1997); Koizumi, M. "ENA oligonucleotides as therapeutics". *Current opinion in molecular therapeutics* 8 (2): 144-149 (2006); and Abramova et al., "Novel oligonucleotide analogues based on morpholino nucleoside subunits-antisense technologies: new chemical possibilities," *Indian Journal of Chemistry* 48B:1721-1726 (2009). Alternatively, the polynucleic acid molecule is produced biologically using an expression vector into which a polynucleic acid molecule has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted polynucleic acid molecule will be of an antisense orientation to a target polynucleic acid molecule of interest).

[0128] In some embodiments, a polynucleic acid molecule is synthesized via a tandem synthesis methodology, wherein both strands are synthesized as a single contiguous oligonucleotide fragment or strand separated by a cleavable linker which is subsequently cleaved to provide separate fragments or strands that hybridize and permit purification of the duplex.

[0129] In some instances, a polynucleic acid molecule is also assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment includes the antisense region of the molecule.

[0130] Additional modification methods for incorporating, for example, sugar, base and phosphate modifications include: Eckstein et al., International Publication PCT No. WO 92/07065; Perrault et al. *Nature.* 1990, 344, 565-568; Pieken et al. *Science.* 1991, 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman et al. International Publication PCT No. WO 93/15187; Sproat, U.S. Pat. No. 5,334,711 and Beigelman et al., 1995, *J. Biol. Chem.*, 270, 25702; Beigelman et al., International PCT publication No. WO 97/26270; Beigelman et al., U.S. Pat. No. 5,716,824; Usman et al., U.S. Pat. No. 5,627,053; Woolf et al., International PCT Publication No. WO 98/13526; Thompson et al., U.S. Ser. No. 60/082,404 which was filed on Apr. 20, 1998; Karpeisky et al., 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina et al., 1997, *Bioorg. Med. Chem.*, 5, 1999-2010. Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis.

[0131] In some instances, while chemical modification of the polynucleic acid molecule internucleotide linkages with

phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications sometimes cause toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages in some cases is minimized. In such cases, the reduction in the concentration of these linkages lowers toxicity, increases efficacy and higher specificity of these molecules.

Polynucleic Acid Molecule Conjugates

[0132] In some embodiments, a polynucleic acid molecule (B) is further conjugated to a polypeptide (A) for delivery to a site of interest. In some instances, at least one polypeptide A is conjugated to at least one B. In some instances, the at least one polypeptide A is conjugated to the at least one B to form an A-B conjugate. In some embodiments, at least one A is conjugated to the 5' terminus of B, the 3' terminus of B, an internal site on B, or in any combinations thereof. In some instances, the at least one polypeptide A is conjugated to at least two B. In some instances, the at least one polypeptide A is conjugated to at least 2, 3, 4, 5, 6, 7, 8, or more B.

[0133] In some cases, a polynucleic acid molecule is conjugated to a polypeptide (A) and optionally a polymeric moiety (C). In some embodiments, at least one polypeptide A is conjugated at one terminus of at least one B while at least one C is conjugated at the opposite terminus of the at least one B to form an A-B-C conjugate. In some instances, at least one polypeptide A is conjugated at one terminus of the at least one B while at least one of C is conjugated at an internal site on the at least one B. In some instances, at least one polypeptide A is conjugated directly to the at least one C. In some instances, the at least one B is conjugated indirectly to the at least one polypeptide A via the at least one C to form an A-C-B conjugate.

[0134] In some instances, at least one B and/or at least one C, and optionally at least one D are conjugated to at least one polypeptide A. In some instances, the at least one B is conjugated at a terminus (e.g., a 5' terminus or a 3' terminus) to the at least one polypeptide A or are conjugated via an internal site to the at least one polypeptide A. In some cases, the at least one C is conjugated either directly to the at least one polypeptide A or indirectly via the at least one B. In some instances, the at least one C is conjugated either at the same terminus as the at least one polypeptide A on B, at opposing terminus from the at least one polypeptide A, or independently at an internal site. In some instances, at least one additional polypeptide A is further conjugated to the at least one polypeptide A, to B, or to C. In additional instances, the at least one D is optionally conjugated either directly or indirectly to the at least one polypeptide A, to the at least one B, or to the at least one C. If directly to the at least one polypeptide A, the at least one D is also optionally conjugated to the at least one B to form an A-D-B conjugate or is optionally conjugated to the at least one B and the at least one C to form an A-D-B-C conjugate. In some instances, the at least one D is directly conjugated to the at least one polypeptide A and indirectly to the at least one B and the at least one C to form a D-A-B-C conjugate. If indirectly to the at least one polypeptide A, the at least one D is also optionally conjugated to the at least one B to form an A-B-D conjugate or is optionally conjugated to the at least one B and the at least one C to form an A-B-D-C

conjugate. In some instances, at least one additional D is further conjugated to the at least one polypeptide A, to B, or to C.

Binding Moiety

[0135] In some embodiments, the binding moiety A is a polypeptide. In some instances, the polypeptide is an antibody or its fragment thereof. In some cases, the fragment is a binding fragment. In some instances, the antibody or antigen binding fragment thereof comprises a humanized antibody or antigen binding fragment thereof, murine antibody or antigen binding fragment thereof, chimeric antibody or antigen binding fragment thereof, monoclonal antibody or antigen binding fragment thereof, a binding fragment having a light chain domain and a heavy chain domain, a binding fragment having two light chain domains and two heavy chain domains, a binding fragment having two or more light chain domains and heavy chain domains, monovalent Fab', divalent Fab₂, F(ab)'₃ fragments, single-chain variable fragment (scFv), bis-scFv, (scFv)₂, diabody, minibody, nanobody, triabody, tetrabody, disulfide stabilized Fv protein (dsFv), single-domain antibody (sdAb), Ig NAR, camelid antibody or antigen binding fragment thereof, bispecific antibody or biding fragment thereof, or a chemically modified derivative thereof.

[0136] In some embodiments, the binding moiety A is a bispecific antibody or antigen binding fragment thereof. In some instances, the bispecific antibody is a trifunctional antibody or a bispecific mini-antibody. In some cases, the bispecific antibody is a trifunctional antibody. In some instances, the trifunctional antibody is a full length monoclonal antibody comprising binding sites for two different antigens.

[0137] In some cases, the bispecific antibody is a bispecific mini-antibody. In some instances, the bispecific mini-antibody comprises divalent Fab₂, F(ab)'₃ fragments, bis-scFv, (scFv)₂, diabody, minibody, triabody, tetrabody or a bi-specific T-cell engager (BiTE). In some embodiments, the bi-specific T-cell engager is a fusion protein that contains two single-chain variable fragments (scFvs) in which the two scFvs target epitopes of two different antigens.

[0138] In some embodiments, the binding moiety A is a bispecific mini-antibody. In some instances, A is a bispecific Fab₂. In some instances, A is a bispecific F(ab)'₃ fragment. In some cases, A is a bispecific bis-scFv. In some cases, A is a bispecific (scFv)₂. In some embodiments, A is a bispecific diabody. In some embodiments, A is a bispecific minibody. In some embodiments, A is a bispecific triabody. In other embodiments, A is a bispecific tetrabody. In other embodiments, A is a bi-specific T-cell engager (BiTE).

[0139] In some embodiments, the binding moiety A is a trispecific antibody. In some instances, the trispecific antibody comprises F(ab)'₃ fragments or a triabody. In some instances, A is a trispecific F(ab)'₃ fragment. In some cases, A is a triabody. In some embodiments, A is a trispecific antibody as described in Dimas, et al., "Development of a trispecific antibody designed to simultaneously and efficiently target three different antigens on tumor cells," *Mol. Pharmaceutics*, 12(9): 3490-3501 (2015).

[0140] In some embodiments, the binding moiety A is an antibody or antigen binding fragment thereof that recognizes a cell surface protein. In some instances, the binding moiety A is an antibody or antigen binding fragment thereof that recognizes a cell surface protein on a muscle cell. In some

cases, the binding moiety A is an antibody or antigen binding fragment thereof that recognizes a cell surface protein on a skeletal muscle cell.

[0141] In some embodiments, exemplary antibodies include, but are not limited to, an anti-myosin antibody, an anti-transferrin receptor antibody, and an antibody that recognizes Muscle-Specific kinase (MuSK). In some instances, the antibody is an anti-transferrin receptor (anti-CD71) antibody.

[0142] In some embodiments, where the antibody is an anti-transferrin receptor (anti-CD71) antibody, the anti-transferrin antibody specifically binds to a transferrin receptor (TfR), preferably, specifically binds to transferrin receptor 1 (TfR1), or more preferably, specifically binds to human transferrin receptor 1 (TfR1) (or human CD71).

[0143] In some instances, the anti-transferrin receptor antibody comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281; HCDR2 sequence EINPIX₁GRSNYAX₂KFQG (SEQ ID NO: 406), wherein X₁ is selected from N or Q and X₂ is selected from Q or E; and HCDR3 sequence comprising SEQ ID NO: 283.

[0144] In some embodiments, the VH region of the anti-transferrin receptor antibody comprises HCDR1, HCDR2, and HCDR3 sequences selected from Table 1.

TABLE 1

Name	SEQ ID NO:		SEQ ID NO:		SEQ ID NO:	
	HCDR1	HCDR2	HCDR2	HCDR3	HCDR3	HCDR3
13E4_VH1	YTFTNYW MH	281 EINPINGRSNY AQKFQG	282	GTRAMHY	283	
13E4_VH2*	YTFTNYW MH	281 EINPINGRSNY AEKFQG	284	GTRAMHY	283	
13E4_VH3	YTFTNYW MH	281 EINPIQGRSNY AEKFQG	285	GTRAMHY	283	

*13E4_VH2 shares the same HCDR1, HCDR2, and HCDR3 sequences with anti-transferrin receptor antibody 13E4_VH4

[0145] In some embodiments, the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281; HCDR2 sequence comprising SEQ ID NO: 282, 284, or 285; and HCDR3 sequence comprising SEQ ID NO: 283. In some instances, the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281, HCDR2 sequence comprising SEQ ID NO: 282, and HCDR3 sequence comprising SEQ ID NO: 283. In some instances, the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281, HCDR2 sequence comprising SEQ ID NO: 284, and HCDR3 sequence comprising SEQ ID NO: 283. In some instances, the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281, HCDR2 sequence comprising SEQ ID NO: 285, and HCDR3 sequence comprising SEQ ID NO: 283.

[0146] In some embodiments, the VL region of the anti-transferrin receptor antibody comprises LCDR1 sequence RTSENIYX₃NLA (SEQ ID NO: 407), LCDR2 sequence AX₄TNLAX₅ (SEQ ID NO: 408), and LCDR3 sequence QHFWGTPLTX₆ (SEQ ID NO: 409), wherein X₃ is selected from N or S, X₄ is selected from A or G, X₅ is selected from D or E, and X₆ is present or absence, and if present, is F.

[0147] In some embodiments, the VL region of the anti-transferrin receptor antibody comprises LCDR1, LCDR2, and LCDR3 sequences selected from Table 2.

TABLE 2

Name	SEQ ID NO:		SEQ ID NO:		SEQ ID NO:	
	LCDR1	LCDR2	LCDR2	LCDR3	LCDR3	LCDR3
13E4_VL1*	RTSENIYN NLA	286	AATNLAD	287	QHFWGTPLT	288
13E4_VL3	RTSENIYN NLA	286	AATNLAE	289	QHFWGTPLTF	290
13E4_VL4	RTSENIYS NLA	291	AGTNLAD	292	QHFWGTPLTF	290

*13E4_VL1 shares the same LCDR1, LCDR2, and LCDR3 sequences with anti-transferrin receptor antibody 13E4_VL2

[0148] In some instances, the VL region comprises LCDR1 sequence RTSENIYX₃NLA (SEQ ID NO: 407), LCDR2 sequence comprising SEQ ID NO: 287, 289, or 292, and LCDR3 sequence comprising SEQ ID NO: 288 or 290, wherein X₃ is selected from N or S.

[0149] In some instances, the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286 or 291, LCDR2 sequence AX₄TNLAX₅ (SEQ ID NO: 408), and LCDR3 sequence comprising SEQ ID NO: 288 or 290, wherein X₄ is selected from A or G, and X₅ is selected from D or E.

[0150] In some instances, the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286 or 291, LCDR2 sequence SEQ ID NO: 287, 289, or 292, and LCDR3 sequence QHFWGTPLTX₆ (SEQ ID NO: 409), wherein X₆ is present or absence, and if present, is F.

[0151] In some instances, the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286, LCDR2 sequence AATNLAX₅ (SEQ ID NO: 410), and LCDR3 sequence QHFWGTPLTX₆ (SEQ ID NO: 409), wherein X₅ is selected from D or E and X₆ is present or absence, and if present, is F.

[0152] In some instances, the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286, LCDR2 sequence comprising SEQ ID NO: 287, and LCDR3 sequence comprising SEQ ID NO: 288.

[0153] In some instances, the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286, LCDR2 sequence comprising SEQ ID NO: 289, and LCDR3 sequence comprising SEQ ID NO: 290.

[0154] In some instances, the VL region comprises LCDR1 sequence comprising SEQ ID NO: 291, LCDR2 sequence comprising SEQ ID NO: 292, and LCDR3 sequence comprising SEQ ID NO: 290.

[0155] In some embodiments, the anti-transferrin receptor antibody comprises a VH region and a VL region, wherein the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281; HCDR2 sequence EINPIX₁GRSNYAX₂KFQG (SEQ ID NO: 406), wherein X₁ is selected from N or Q and X₂ is selected from Q or E; and HCDR3 sequence comprising SEQ ID NO: 283; and the VL region comprises LCDR1 sequence RTSENIYX₃NLA (SEQ ID NO: 407), LCDR2 sequence AX₄TNLAX₅ (SEQ ID NO: 408), and LCDR3 sequence QHFWGTPLTX₆ (SEQ ID NO: 409), wherein X₃

ID NO: 281, HCDR2 sequence comprising SEQ ID NO: 285, and HCDR3 sequence comprising SEQ ID NO: 283; and the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286, LCDR2 sequence comprising SEQ ID NO: 287, and LCDR3 sequence comprising SEQ ID NO: 288.

[0182] In some instances, the anti-transferrin receptor antibody comprises a VH region and a VL region, in which the VH region comprises HCDR1 sequence comprising SEQ ID NO: 281, HCDR2 sequence comprising SEQ ID NO: 285, and HCDR3 sequence comprising SEQ ID NO: 283; and the VL region comprises LCDR1 sequence comprising SEQ ID NO: 286, LCDR2 sequence comprising SEQ ID NO: 289, and LCDR3 sequence comprising SEQ ID NO: 290.

[0183] In some instances, the anti-transferrin receptor antibody comprises a VH region and a VL region, in which the VH region comprises HCDR1 sequence comprising SEQ

ID NO: 281, HCDR2 sequence comprising SEQ ID NO: 285, and HCDR3 sequence comprising SEQ ID NO: 283; and the VL region comprises LCDR1 sequence comprising SEQ ID NO: 291, LCDR2 sequence comprising SEQ ID NO: 292, and LCDR3 sequence comprising SEQ ID NO: 290.

[0184] In some embodiments, the anti-transferrin receptor antibody comprises a VH region and a VL region in which the sequence of the VH region comprises about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 293-296 and the sequence of the VL region comprises about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 298-301.

[0185] In some embodiments, the VH region comprises a sequence selected from SEQ ID NOs: 293-296 (Table 3) and the VL region comprises a sequence selected from SEQ ID NOs: 298-301 (Table 4). The underlined regions in Table 3 and Table 4 denote the respective CDR1, CDR2, or CDR3 sequence.

TABLE 3

NAME	VH SEQUENCE	SEQ ID NO:
13E4_VH1	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLEW</u> MGEINPINGSRNYA <u>QKFGQGRVTLTVDT</u> SI STAYMELSRLSDDTAVY YCARGTRAMHYWGQGLTVTVSS	293
13E4_VH2	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLEW</u> IGEINPINGSRNYA <u>EKFGQGRVTLTVDT</u> SS STAYMELSRLSDDTAVY YCARGTRAMHYWGQGLTVTVSS	294
13E4_VH3	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLEW</u> MGEINP <u>IQGRS</u> NYA <u>EKFGQGRVTLTVDT</u> SS STAYMELSSLRSEDTATY YCARGTRAMHYWGQGLTVTVSS	295
13E4_VH4	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLEW</u> MGEINPINGSRNYA <u>EKFGQGRVTLTVDT</u> SS STAYMELSSLRSEDTATY YCARGTRAMHYWGQGLTVTVSS	296
13E4_VH	QVQLQQPGAELVKPGASVKLSCKASGYTF <u>TNYWMHWVKQRPGQGLEW</u> IGEINPINGSRNYGERF <u>TKATLTVDK</u> SS STAYMQLSSLTSEDSAVY YCARGTRAMHYWGQGSVTVSS	297

TABLE 4

NAME	VL SEQUENCE	SEQ ID NO:
13E4_VL1	DIQMTQSPSSLSASVGDRTVITCRTESEN <u>YNNLAWYQQKPKGKSPKLLIYA</u> <u>TNLDAGVPSRFSGSGSDYTLTISSLPEDFATYYCQHF</u> WGTP ¹ LFGGG KVEIK	298
13E4_VL2	DIQMTQSPSSLSASVGDRTVITCRTESEN <u>YNNLAWYQQKPKGKAPKLLIYA</u> <u>ATNLDAGVPSRFSGSGSDYTLTISSLPEDFATYYCQHF</u> WGTP ¹ LFGG GTKVEIK	299
13E4_VL3	DIQMTQSPSSLSASVGDRTVITCRTESEN <u>YNNLAWYQQKPKGKAPKLLIYA</u> <u>ATNLAEGVPSRFSGSGSDYTLTISSLPEDFATYYCQHF</u> WGTP ¹ LFGGG TKVEIK	300
13E4_VL4	DIQMTQSPSSLSASVGDRTVITCRTESEN <u>YNNLAWYQQKPKGKAPKLLIYA</u> <u>TNLDAGVPSRFSGSGSDYTLTISSLPEDFANYYCQHF</u> WGTP ¹ LFGGG TKVEIK	301
13E4_VL	DIQMTQSPASLSVSVGETVITCRTESEN <u>YNNLAWYQQKQKSPQLLYYA</u> <u>ATNLDAGVPSRFSGSGDQYSLKINLSQSEDFGNYYCQHF</u> WGTP ¹ LFGA GTKLELK	302

[0186] In some embodiments, the anti-transferrin receptor antibody comprises a VH region and a VL region as illustrated in Table 5.

TABLE 5

	13E4_VH1 (SEQ ID NO: 13)	13E4_VH2 (SEQ ID NO: 14)	13E4_VH3 (SEQ ID NO: 15)	13E4_VH4 (SEQ ID NO: 16)
13E4_VL1 (SEQ ID NO: 298)	SEQ ID NO: 293 + SEQ ID NO: 298	SEQ ID NO: 294 + SEQ ID NO: 298	SEQ ID NO: 295 + SEQ ID NO: 298	SEQ ID NO: 296 + SEQ ID NO: 298
13E4_VL2 (SEQ ID NO: 299)	SEQ ID NO: 293 + SEQ ID NO: 299	SEQ ID NO: 294 + SEQ ID NO: 299	SEQ ID NO: 295 + SEQ ID NO: 299	SEQ ID NO: 296 + SEQ ID NO: 299
13E4_VL3 (SEQ ID NO: 300)	SEQ ID NO: 293 + SEQ ID NO: 300	SEQ ID NO: 294 + SEQ ID NO: 300	SEQ ID NO: 295 + SEQ ID NO: 300	SEQ ID NO: 296 + SEQ ID NO: 300
13E4_VL4 (SEQ ID NO: 301)	SEQ ID NO: 293 + SEQ ID NO: 301	SEQ ID NO: 294 + SEQ ID NO: 301	SEQ ID NO: 295 + SEQ ID NO: 301	SEQ ID NO: 296 + SEQ ID NO: 301

[0187] In some embodiments, an anti-transferrin receptor antibody described herein comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some instances, the anti-transferrin receptor antibody comprises an IgG framework (e.g., IgG1, IgG2, IgG3, or IgG4). In some cases, the anti-transferrin receptor antibody comprises an IgG1 framework. In some cases, the anti-transferrin receptor antibody comprises an IgG2 (e.g., an IgG2a or IgG2b) framework. In some cases, the anti-transferrin receptor antibody comprises an IgG2a framework. In some cases, the anti-transferrin receptor antibody comprises an IgG2b framework. In some cases, the anti-transferrin receptor antibody comprises an IgG3 framework. In some cases, the anti-transferrin receptor antibody comprises an IgG4 framework.

[0188] In some cases, an anti-transferrin receptor antibody comprises one or more mutations in a framework region, e.g., in the CH1 domain, CH2 domain, CH3 domain, hinge region, or a combination thereof. In some instances, the one or more mutations are to stabilize the antibody and/or to increase half-life. In some instances, the one or more mutations are to modulate Fc receptor interactions, to reduce or eliminate Fc effector functions such as FcγR, antibody-dependent cell-mediated cytotoxicity (ADCC), or complement-dependent cytotoxicity (CDC). In additional instances, the one or more mutations are to modulate glycosylation.

[0189] In some embodiments, the one or more mutations are located in the Fc region. In some instances, the Fc region comprises a mutation at residue position L234, L235, or a combination thereof. In some instances, the mutations comprise L234 and L235. In some instances, the mutations comprise L234A and L235A. In some cases, the residue positions are in reference to IgG1.

[0190] In some instances, the Fc region comprises a mutation at residue position L234, L235, D265, N297, K322, L328, or P329, or a combination thereof. In some instances, the mutations comprise L234 and L235 in combination with a mutation at residue position K322, L328, or P329. In some cases, the Fc region comprises mutations at L234, L235, and K322. In some cases, the Fc region comprises mutations at L234, L235, and L328. In some cases, the Fc region com-

prises mutations at L234, L235, and P329. In some cases, the Fc region comprises mutations at D265 and N297. In some cases, the residue position is in reference to IgG1.

[0191] In some instances, the Fc region comprises L234A, L235A, D265A, N297G, K322G, L328R, or P329G, or a combination thereof. In some instances, the Fc region comprises L234A and L235A in combination with K322G, L328R, or P329G. In some cases, the Fc region comprises L234A, L235A, and K322G. In some cases, the Fc region comprises L234A, L235A, and L328R. In some cases, the Fc region comprises L234A, L235A, and P329G. In some cases, the Fc region comprises D265A and N297G. In some cases, the residue position is in reference to IgG1.

[0192] In some instances, the Fc region comprises a mutation at residue position L235, L236, D265, N297, K322, L328, or P329, or a combination of the mutations. In some instances, the Fc region comprises mutations at L235 and L236. In some instances, the Fc region comprises mutations at L235 and L236 in combination with a mutation at residue position K322, L328, or P329. In some cases, the Fc region comprises mutations at L235, L236, and K322. In some cases, the Fc region comprises mutations at L235, L236, and L328. In some cases, the Fc region comprises mutations at L235, L236, and P329. In some cases, the Fc region comprises mutations at D265 and N297. In some cases, the residue position is in reference to IgG2b.

[0193] In some embodiments, the Fc region comprises L235A, L236A, D265A, N297G, K322G, L328R, or P329G, or a combination thereof. In some instances, the Fc region comprises L235A and L236A. In some instances, the Fc region comprises L235A and L236A in combination with K322G, L328R, or P329G. In some cases, the Fc region comprises L235A, L236A, and K322G. In some cases, the Fc region comprises L235A, L236A, and L328R. In some cases, the Fc region comprises L235A, L236A, and P329G. In some cases, the Fc region comprises D265A and N297G. In some cases, the residue position is in reference to IgG2b.

[0194] In some embodiments, the Fc region comprises a mutation at residue position L233, L234, D264, N296, K321, L327, or P328, wherein the residues correspond to positions 233, 234, 264, 296, 321, 327, and 328 of SEQ ID NO: 303. In some instances, the Fc region comprises mutations at L233 and L234. In some instances, the Fc region comprises mutations at L233 and L234 in combination with a mutation at residue position K321, L327, or P328. In some cases, the Fc region comprises mutations at L233, L234, and K321. In some cases, the Fc region comprises mutations at L233, L234, and L327. In some cases, the Fc region comprises mutations at L233, L234, and K321. In some cases, the Fc region comprises mutations at L233, L234, and P328. In some instances, the Fc region comprises mutations at D264 and N296. In some cases, equivalent positions to residue L233, L234, D264, N296, K321, L327, or P328 in an IgG1, IgG2, IgG3, or IgG4 framework are contemplated. In some cases, mutations to a residue that corresponds to residue L233, L234, D264, N296, K321, L327, or P328 of SEQ ID NO: 23 in an IgG1, IgG2, or IgG4 framework are also contemplated.

[0195] In some embodiments, the Fc region comprises L233A, L234A, D264A, N296G, K321G, L327R, or P328G, wherein the residues correspond to positions 233, 234, 264, 296, 321, 327, and 328 of SEQ ID NO: 303. In some instances, the Fc region comprises L233A and L234A. In some instances, the Fc region comprises L233A and

L234A in combination with K321G, L327R, or P328G. In some cases, the Fc region comprises L233A, L234A, and K321G. In some cases, the Fc region comprises L233A, L234A, and L327R. In some cases, the Fc region comprises L233A, L234A, and K321G. In some cases, the Fc region comprises L233A, L234A, and P328G. In some instances, the Fc region comprises D264A and N2% G.

[0196] In some embodiments, the human IgG constant region is modified to alter antibody-dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC), e.g., with an amino acid modification described in Natsume et al., 2008 *Cancer Res*, 68(10): 3863-72; Idusogie et al., 2001 *J Immunol*, 166(4): 2571-5; Moore et

al., 2010 *mAbs*, 2(2): 181-189; Lazar et al., 2006 *PNAS*, 103(11): 4005-4010; Shields et al., 2001 *JBC*, 276(9): 6591-6604; Stavenhagen et al., 2007 *Cancer Res*, 67(18): 8882-8890; Stavenhagen et al., 2008 *Advan. Enzyme Regul.*, 48: 152-164; Alegre et al., 1992 *J Immunol*, 148: 3461-3468; Reviewed in Kaneko and Niwa, 2011 *Biodrugs*, 25(1): 1-11. [0197] In some embodiments, an anti-transferrin receptor antibody described herein is a full-length antibody, comprising a heavy chain (HC) and a light chain (LC). In some cases, the heavy chain (HC) comprises a sequence selected from Table 6. In some cases, the light chain (LC) comprises a sequence selected from Table 7. The underlined region denotes the respective CDRs.

TABLE 6

NAME	HC SEQUENCE	SEQ ID NO:
13E4_VH1	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLE</u> WMGEINP <u>INGRSNYAQKFKQGRVTLTVD</u> TSISTAYMELSRRLSDDTAVY YCARGTRAMHYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELGGPSVF LFPKPKDITLMIKSRTEPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIK KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPG	303
13E4_VH1_a	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLE</u> WMGEINP <u>INGRSNYAQKFKQGRVTLTVD</u> TSISTAYMELSRRLSDDTAVY YCARGTRAMHYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPEAAGGPSVF LFPKPKDITLMIKSRTEPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIK KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPG	304
13E4_VH1_b	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLE</u> WMGEINP <u>INGRSNYAQKFKQGRVTLTVD</u> TSISTAYMELSRRLSDDTAVY YCARGTRAMHYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPEAAGGPSVF LFPKPKDITLMIKSRTEPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCGVSNKALPAPIEKTIK KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPG	305
13E4_VH1_c	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLE</u> WMGEINP <u>INGRSNYAQKFKQGRVTLTVD</u> TSISTAYMELSRRLSDDTAVY YCARGTRAMHYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPEAAGGPSVF LFPKPKDITLMIKSRTEPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAIEKTIK KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPG	306
13E4_VH1_d	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLE</u> WMGEINP <u>INGRSNYAQKFKQGRVTLTVD</u> TSISTAYMELSRRLSDDTAVY YCARGTRAMHYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPEAAGGPSVF LFPKPKDITLMIKSRTEPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTIK KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPG	307
13E4_VH1_e	QVQLVQSGAEVKKPGASVKVSCKASGYTF <u>TNYWMHWVRQAPGQGLE</u> WMGEINP <u>INGRSNYAQKFKQGRVTLTVD</u> TSISTAYMELSRRLSDDTAVY	308

TABLE 6-continued

NAME	HC SEQUENCE	SEQ ID NO:
	YCARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS LGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK KPREEQYGSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKLSLSLSPG	
13E4_VH2	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGGGLE WIGEIINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSRRLRSDDTAVYY CARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS GTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK PREEQYNSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH HYTQKLSLSLSPG	309
13E4_VH2_a	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGGGLE WIGEIINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSRRLRSDDTAVYY CARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS GTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAAGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK PREEQYNSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH HYTQKLSLSLSPG	310
13E4_VH2_b	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGGGLE WIGEIINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSRRLRSDDTAVYY CARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS GTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAAGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK PREEQYNSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH HYTQKLSLSLSPG	311
13E4_VH2_c	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGGGLE WIGEIINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSRRLRSDDTAVYY CARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS GTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAAGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK PREEQYNSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH HYTQKLSLSLSPG	312
13E4_VH2_d	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGGGLE WIGEIINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSRRLRSDDTAVYY CARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS GTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEAAGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK PREEQYNSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH HYTQKLSLSLSPG	313
13E4_VH2_e	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGGGLE WIGEIINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSRRLRSDDTAVYY CARGTRAMHYWGQGLVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYLSLSSVTVPS GTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPELLGGPSV LPPPKPDLMIKSRTPPEVTCVVAVSHEDPEVKFNWYVDGVEVHNAK PREEQYNSYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH HYTQKLSLSLSPG	314

TABLE 6-continued

NAME	HC SEQUENCE	SEQ ID NO:
13E4_VH3	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPIQGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPELLGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHN HVTQKSLSLSPG</p>	315
13E4_VH3_a	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPIQGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHN HVTQKSLSLSPG</p>	316
13E4_VH3_b	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPIQGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCGVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHN HVTQKSLSLSPG</p>	317
13E4_VH3_c	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPIQGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHN HVTQKSLSLSPG</p>	318
13E4_VH3_d	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPIQGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALGAP IEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHN HVTQKSLSLSPG</p>	319
13E4_VH3_e	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPIQGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPELLGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHN HVTQKSLSLSPG</p>	320
13E4_VH4	<p>QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWRQAPGQGLE WMGEINPINGRSNYAEKFKQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEPKS CDKHTHTCPPCPAPELLGGPSVFL FPPKPKDTLMI SRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK</p>	321

TABLE 6-continued

NAME	HC SEQUENCE	SEQ ID NO :
	AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN HYTQKSLSLSPG	
13E4_VH4_a	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGQGLE WMGEINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSYRIVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN HYTQKSLSLSPG	322
13E4_VH4_b	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGQGLE WMGEINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSYRIVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN HYTQKSLSLSPG	323
13E4_VH4_c	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGQGLE WMGEINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSYRIVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN HYTQKSLSLSPG	324
13E4_VH4_d	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGQGLE WMGEINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSYRIVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN HYTQKSLSLSPG	325
13E4_VH4_e	QVQLVQSGAEVKKPGASVKVSCASGYTFITNYMHWRQAPGQGLE WMGEINPINGRSNYAEKFGQGRVTLTVDTSSSTAYMELSSLRSEDTATYY CARGTRAMHYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSVVTVPSSSL GTQTYI CNVNHKPSNTKVDKRVPEKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMI SRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYGSYRIVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHN HYTQKSLSLSPG	326

TABLE 7

NAME	LC SEQUENCE	SEQ ID NO :
13E4_VL1	DIQMTQSPSSLSASVGRVTITCRTESENINYNLAWYQQKPKGKSPKLLIYA ATNLADGVPSRFGSGSGSDYTLTISLQPEDFATYYCQHPWGTPLTFG GGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNMFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC	327

TABLE 7-continued

NAME	LC SEQUENCE	SEQ ID NO:
1.3E4_VL2	DIQMTQSPSSLSASVGRVTITCR TS ENIYNNLAWYQQKPKAPKLLIY AATNLADGVPSRFRSGSGSDYTLTISSLQPEDFATYYCQHFWGTP LF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSYLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	328
1.3E4_VL3	DIQMTQSPSSLSASVGRVTITCR TS ENIYNNLAWYQQKPKAPKLLIY AATNLAE G VP S RFRSGSGSDYTLTISSLQPEDFATYYCQHFWGTP LF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSYLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	329
1.3E4_VL4	DIQMTQSPSSLSASVGRVTITCR TS ENIY S NLAWYQQKPKAPKLLIY A GTNLADGVPSRFRSGSGSDYTLTISSLQPEDFANYYCQHFWGTP LF GGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSYLSSTLTLSKADY E KHKVYACEV THQGLSSPVTKSFNRGEC	330

[0198] In some embodiments, an anti-transferrin receptor antibody described herein has an improved serum half-life compared to a reference anti-transferrin receptor antibody. In some instances, the improved serum half-life is at least 30 minutes, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 12 hours, 18 hours, 24 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 30 days, or longer than reference anti-transferrin receptor antibody.

[0199] In some embodiments, the binding moiety A is conjugated to a polynucleic acid molecule (B) non-specifically. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) via a lysine residue or a cysteine residue, in a non-site specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) via a lysine residue (e.g., lysine residue present in the binding moiety A) in a non-site specific manner. In some cases, the binding moiety A is conjugated to a polynucleic acid molecule (B) via a cysteine residue (e.g., cysteine residue present in the binding moiety A) in a non-site specific manner.

[0200] In some embodiments, the binding moiety A is conjugated to a polynucleic acid molecule (B) in a site-specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) through a lysine residue, a cysteine residue, at the 5'-terminus, at the 3'-terminus, an unnatural amino acid, or an enzyme-modified or enzyme-catalyzed residue, via a site-specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) through a lysine residue (e.g., lysine residue present in the binding moiety A) via a site-specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) through a cysteine residue (e.g., cysteine residue present in the binding moiety A) via a site-specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) at the 5'-terminus via a site-specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) at the 3'-terminus via a site-specific manner. In some instances, the binding moiety A is conjugated to a polynucleic acid molecule (B) through an unnatural amino acid via a site-specific manner. In some instances, the binding moiety A is conju-

gated to a polynucleic acid molecule (B) through an enzyme-modified or enzyme-catalyzed residue via a site-specific manner.

[0201] In some embodiments, one or more polynucleic acid molecule (B) is conjugated to a binding moiety A. In some instances, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or more polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 1 polynucleic acid molecule is conjugated to one binding moiety A. In some instances, about 2 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 3 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 4 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 5 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 6 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 7 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 8 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 9 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 10 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 11 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 12 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 13 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 14 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 15 polynucleic acid molecules are conjugated to one binding moiety A. In some instances, about 16 polynucleic acid molecules are conjugated to one binding moiety A. In some cases, the one or more polynucleic acid molecules are the same. In other cases, the one or more polynucleic acid molecules are different.

[0202] In some embodiments, the number of polynucleic acid molecule (B) conjugated to a binding moiety A forms a ratio. In some instances, the ratio is referred to as a DAR (drug-to-antibody) ratio, in which the drug as referred to herein is the polynucleic acid molecule (B). In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or greater. In some instances, the DAR

ratio of the polynucleic acid molecule (B) to binding moiety A is about 1 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 2 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 3 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 4 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 5 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 6 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 7 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 8 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 9 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 10 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 11 or greater. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 12 or greater.

[0203] In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 1. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 2. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 3. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 4. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 5. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 6. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 7. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 8. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 9. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 10. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 11. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 12. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 13. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 14. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 15. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is about 16.

[0204] In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 1. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 2. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 4. In some instances, the

DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 6. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 8. In some instances, the DAR ratio of the polynucleic acid molecule (B) to binding moiety A is 12.

[0205] In some instances, a conjugate comprising polynucleic acid molecule (B) and binding moiety A has improved activity as compared to a conjugate comprising polynucleic acid molecule (B) without a binding moiety A. In some instances, improved activity results in enhanced biologically relevant functions, e.g., improved stability, affinity, binding, functional activity, and efficacy in treatment or prevention of a disease state. In some instances, the disease state is a result of one or more mutated exons of a gene. In some instances, the conjugate comprising polynucleic acid molecule (B) and binding moiety A results in increased exon skipping of the one or more mutated exons as compared to the conjugate comprising polynucleic acid molecule (B) without a binding moiety A. In some instances, exon skipping is increased by at least or about 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more than 95% in the conjugate comprising polynucleic acid molecule (B) and binding moiety A as compared to the conjugate comprising polynucleic acid molecule (B) without a binding moiety A.

[0206] In some embodiments, an antibody or antigen binding fragment is further modified using conventional techniques known in the art, for example, by using amino acid deletion, insertion, substitution, addition, and/or by recombination and/or any other modification (e.g., post-translational and chemical modifications, such as glycosylation and phosphorylation) known in the art either alone or in combination. In some instances, the modification further comprises a modification for modulating interaction with Fc receptors. In some instances, the one or more modifications include those described in, for example, International Publication No. WO97/34631, which discloses amino acid residues involved in the interaction between the Fc domain and the FcRn receptor. Methods for introducing such modifications in the nucleic acid sequence underlying the amino acid sequence of an antibody or antigen binding fragment is well known to the person skilled in the art.

[0207] In some instances, an antigen binding fragment further encompasses its derivatives and includes polypeptide sequences containing at least one CDR.

[0208] In some instances, the term “single-chain” as used herein means that the first and second domains of a bispecific single chain construct are covalently linked, preferably in the form of a co-linear amino acid sequence encodable by a single nucleic acid molecule.

[0209] In some instances, a bispecific single chain antibody construct relates to a construct comprising two antibody derived binding domains. In such embodiments, bispecific single chain antibody construct is tandem bi-scFv or diabody. In some instances, a scFv contains a VH and VL domain connected by a linker peptide. In some instances, linkers are of a length and sequence sufficient to ensure that each of the first and second domains can, independently from one another, retain their differential binding specificities.

[0210] In some embodiments, binding to or interacting with as used herein defines a binding/interaction of at least two antigen-interaction-sites with each other. In some instances, antigen-interaction-site defines a motif of a poly-

peptide that shows the capacity of specific interaction with a specific antigen or a specific group of antigens. In some cases, the binding/interaction is also understood to define a specific recognition. In such cases, specific recognition refers to that the antibody or its antigen binding fragment is capable of specifically interacting with and/or binding to at least two amino acids of each of a target molecule. For example, specific recognition relates to the specificity of the antibody molecule, or to its ability to discriminate between the specific regions of a target molecule. In additional instances, the specific interaction of the antigen-interaction-site with its specific antigen results in an initiation of a signal, e.g. due to the induction of a change of the conformation of the antigen, an oligomerization of the antigen, etc. In further embodiments, the binding is exemplified by the specificity of a "key-lock-principle". Thus in some instances, specific motifs in the amino acid sequence of the antigen-interaction-site and the antigen bind to each other as a result of their primary, secondary or tertiary structure as well as the result of secondary modifications of said structure. In such cases, the specific interaction of the antigen-interaction-site with its specific antigen results as well in a simple binding of the site to the antigen.

[0211] In some instances, specific interaction further refers to a reduced cross-reactivity of the antibody or antigen binding fragment or a reduced off-target effect. For example, the antibody or antigen binding fragment that bind to the polypeptide/protein of interest but do not or do not essentially bind to any of the other polypeptides are considered as specific for the polypeptide/protein of interest. Examples for the specific interaction of an antigen-interaction-site with a specific antigen comprise the specificity of a ligand for its receptor, for example, the interaction of an antigenic determinant (epitope) with the antigenic binding site of an antibody.

Additional Binding Moieties

[0212] In some embodiments, the binding moiety is a plasma protein. In some instances, the plasma protein comprises albumin. In some instances, the binding moiety A is albumin. In some instances, albumin is conjugated by one or more of a conjugation chemistry described herein to a polynucleic acid molecule. In some instances, albumin is conjugated by native ligation chemistry to a polynucleic acid molecule. In some instances, albumin is conjugated by lysine conjugation to a polynucleic acid molecule.

[0213] In some instances, the binding moiety is a steroid. Exemplary steroids include cholesterol, phospholipids, di- and triacylglycerols, fatty acids, hydrocarbons that are saturated, unsaturated, comprise substitutions, or combinations thereof. In some instances, the steroid is cholesterol. In some instances, the binding moiety is cholesterol. In some instances, cholesterol is conjugated by one or more of a conjugation chemistry described herein to a polynucleic acid molecule. In some instances, cholesterol is conjugated by native ligation chemistry to a polynucleic acid molecule. In some instances, cholesterol is conjugated by lysine conjugation to a polynucleic acid molecule.

[0214] In some instances, the binding moiety is a polymer, including but not limited to polynucleic acid molecule aptamers that bind to specific surface markers on cells. In this instance the binding moiety is a polynucleic acid that does not hybridize to a target gene or mRNA, but instead is

capable of selectively binding to a cell surface marker similarly to an antibody binding to its specific epitope of a cell surface marker.

[0215] In some cases, the binding moiety is a peptide. In some cases, the peptide comprises between about 1 and about 3 kDa. In some cases, the peptide comprises between about 1.2 and about 2.8 kDa, about 1.5 and about 2.5 kDa, or about 1.5 and about 2 kDa. In some instances, the peptide is a bicyclic peptide. In some cases, the bicyclic peptide is a constrained bicyclic peptide. In some instances, the binding moiety is a bicyclic peptide (e.g., bicycles from Bicycle Therapeutics).

[0216] In additional cases, the binding moiety is a small molecule. In some instances, the small molecule is an antibody-recruiting small molecule. In some cases, the antibody-recruiting small molecule comprises a target-binding terminus and an antibody-binding terminus, in which the target-binding terminus is capable of recognizing and interacting with a cell surface receptor. For example, in some instances, the target-binding terminus comprising a glutamate urea compound enables interaction with PSMA, thereby, enhances an antibody interaction with a cell that expresses PSMA. In some instances, a binding moiety is a small molecule described in Zhang et al., "A remote arene-binding site on prostate specific membrane antigen revealed by antibody-recruiting small molecules," *J Am Chem Soc.* 132(36): 12711-12716 (2010); or McEnaney, et al., "Antibody-recruiting molecules: an emerging paradigm for engaging immune function in treating human disease," *ACS Chem Biol.* 7(7): 1139-1151 (2012).

Production of Antibodies or Antigen Binding Fragment Thereof

[0217] In some embodiments, polypeptides described herein (e.g., antibodies and antigen binding fragments) are produced using any method known in the art to be useful for the synthesis of polypeptides (e.g., antibodies), in particular, by chemical synthesis or by recombinant expression, and are preferably produced by recombinant expression techniques.

[0218] In some instances, an antibody or antigen binding fragment thereof is expressed recombinantly, and the nucleic acid encoding the antibody or antigen binding fragment is assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., 1994. *BioTechniques* 17:242), which involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligation of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0219] Alternatively, a nucleic acid molecule encoding an antibody is optionally generated from a suitable source (e.g., an antibody cDNA library, or cDNA library generated from any tissue or cells expressing the immunoglobulin) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence.

[0220] In some instances, an antibody or its antigen binding is optionally generated by immunizing an animal, such as a rabbit, to generate polyclonal antibodies or, more preferably, by generating monoclonal antibodies, e.g., as described by Kohler and Milstein (1975. *Nature* 256:495-497) or, as described by Kozbor et al. (1983. *Immunology Today* 4:72) or Cole et al. (1985 in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96). Alter-

natively, a clone encoding at least the Fab portion of the antibody is optionally obtained by screening Fab expression libraries (e.g., as described in Huse et al., 1989. *Science* 246:1275-1281) for clones of Fab fragments that bind the specific antigen or by screening antibody libraries (See, e.g., Clackson et al., 1991. *Nature* 352:624; Hane et al., 1997 *Proc. Natl. Acad. Sci. USA* 94:4937).

[0221] In some embodiments, techniques developed for the production of “chimeric antibodies” (Morrison et al., 1984, *Proc. Natl. Acad. Sci.* 81:851-855; Neuberger et al., 1984. *Nature* 312:604-608; Takeda et al., 1985, *Nature* 314:452-454) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity are used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region, e.g., humanized antibodies.

[0222] In some embodiments, techniques described for the production of single chain antibodies (U.S. Pat. No. 4,694, 778; Bird, 1988. *Science* 242:423-42; Huston et al., 1988. *Proc. Natl. Acad. Sci. USA* 85:5879-5883; and Ward et al., 1989. *Nature* 334:544-54) are adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* are also optionally used (Skerra et al., 1988. *Science* 242:1038-1041).

[0223] In some embodiments, an expression vector comprising the nucleotide sequence of an antibody or the nucleotide sequence of an antibody is transferred to a host cell by conventional techniques (e.g., electroporation, liposomal transfection, and calcium phosphate precipitation), and the transfected cells are then cultured by conventional techniques to produce the antibody. In specific embodiments, the expression of the antibody is regulated by a constitutive, an inducible or a tissue, specific promoter.

[0224] In some embodiments, a variety of host-expression vector systems is utilized to express an antibody or its antigen binding fragment described herein. Such host-expression systems represent vehicles by which the coding sequences of the antibody is produced and subsequently purified, but also represent cells that are, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody or its antigen binding fragment in situ. These include, but are not limited to, microorganisms such as bacteria (e.g. *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing an antibody or its antigen binding fragment coding sequences; yeast (e.g., *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing an antibody or its antigen binding fragment coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing an antibody or its antigen binding fragment coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus (CaMV) and tobacco mosaic virus (TMV)) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing an antibody or its antigen binding fragment coding sequences; or mammalian

cell systems (e.g., COS, CHO, BH, 293, 293T, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g. the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[0225] For long-term, high-yield production of recombinant proteins, stable expression is preferred. In some instances, cell lines that stably express an antibody are optionally engineered. Rather than using expression vectors that contain viral origins of replication, host cells are transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells are then allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci that in turn are cloned and expanded into cell lines. This method can advantageously be used to engineer cell lines which express the antibody or its antigen binding fragments.

[0226] In some instances, a number of selection systems are used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., 1977, *Cell* 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 192, *Proc. Natl. Acad. Sci. USA* 48:202), and adenine phosphoribosyltransferase (Lowy et al., 1980, *Cell* 22:817) genes are employed in tk-, hgpri- or aprt-cells, respectively. Also, antimetabolite resistance are used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:357; O'Hare et al., 1981, *Proc. Natl. Acad. Sci. USA* 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, *Proc. Natl. Acad. Sci. USA* 78:2072); neo, which confers resistance to the aminoglycoside G-418 (*Clinical Pharmacology* 12:488-505; Wu and Wu, 1991, *Biotherapy* 3:87-95; Tolstoshev, 1993. *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, 1993. *Science* 260:926-932; and Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; May, 1993. *TIB TECH* 11(5):155-215) and hygromycin (Santerre et al., 1984, *Gene* 30:147). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds., 1993, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY; Kriegler, 1990, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY; and in Chapters 12 and 13, Dracopoli et al. (eds), 1994, *Current Protocols in Human Genetics*, John Wiley & Sons, NY.; Colberre-Garapin et al., 1981, *J. Mol. Biol.* 150:1).

[0227] In some instances, the expression levels of an antibody are increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol. 3. (Academic Press, New York, 1987)). When a marker in the vector system expressing an antibody is amplifiable, an increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the nucleotide sequence of the

antibody, production of the antibody will also increase (Crouse et al., 1983, *Mol. Cell Biol.* 3:257).

[0228] In some instances, any method known in the art for purification or analysis of an antibody or antibody conjugates is used, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Exemplary chromatography methods included, but are not limited to, strong anion exchange chromatography, hydrophobic interaction chromatography, size exclusion chromatography, and fast protein liquid chromatography.

Conjugation Chemistry

[0229] In some embodiments, a polynucleic acid molecule B is conjugated to a binding moiety. In some embodiments, a polynucleic acid molecule B is conjugated to a binding moiety in a formula A-X-B (X is a linker conjugating A and B). In some instances, the binding moiety comprises amino acids, peptides, polypeptides, proteins, antibodies, antigens, toxins, hormones, lipids, nucleotides, nucleosides, sugars, carbohydrates, polymers such as polyethylene glycol and polypropylene glycol, as well as analogs or derivatives of all of these classes of substances. Additional examples of binding moiety also include steroids, such as cholesterol, phospholipids, di- and triacylglycerols, fatty acids, hydrocarbons (e.g., saturated, unsaturated, or contains substitutions), enzyme substrates, biotin, digoxigenin, and polysaccharides. In some instances, the binding moiety is an antibody or antigen binding fragment thereof. In some instances, the polynucleic acid molecule is further conjugated to a polymer, and optionally an endosomolytic moiety.

[0230] In some embodiments, the polynucleic acid molecule is conjugated to the binding moiety by a chemical ligation process. In some instances, the polynucleic acid molecule is conjugated to the binding moiety by a native ligation. In some instances, the conjugation is as described in: Dawson, et al. "Synthesis of proteins by native chemical ligation." *Science* 1994, 266, 776-779; Dawson, et al. "Modulation of Reactivity in Native Chemical Ligation through the Use of Thiol Additives," *J. Am. Chem. Soc.* 1997, 119, 4325-4329; Hackeng, et al. "Protein synthesis by native chemical ligation: Expanded scope by using straightforward methodology," *Proc. Natl. Acad. Sci. USA* 1999, 96, 10068-10073; or Wu, et al. "Building complex glycopeptides: Development of a cysteine-free native chemical ligation protocol," *Angew. Chem. Int. Ed.* 2006, 45, 4116-4125. In some instances, the conjugation is as described in U.S. Pat. No. 8,936,910. In some embodiments, the polynucleic acid molecule is conjugated to the binding moiety either site-specifically or non-specifically via native ligation chemistry.

[0231] In some instances, the polynucleic acid molecule is conjugated to the binding moiety by a site-directed method utilizing a "traceless" coupling technology (Philochem). In some instances, the "traceless" coupling technology utilizes an N-terminal 1,2-aminothiol group on the binding moiety which is then conjugate with a polynucleic acid molecule containing an aldehyde group. (see Casi et al., "Site-specific traceless coupling of potent cytotoxic drugs to recombinant antibodies for pharmacodelivery," *JACS* 134(13): 5887-5892 (2012))

[0232] In some instances, the polynucleic acid molecule is conjugated to the binding moiety by a site-directed method utilizing an unnatural amino acid incorporated into the binding moiety. In some instances, the unnatural amino acid comprises p-acetylphenylalanine (pAcPhe). In some instances, the keto group of pAcPhe is selectively coupled to an alkoxy-amine derivatived conjugating moiety to form an oxime bond. (see Axup et al., "Synthesis of site-specific antibody-drug conjugates using unnatural amino acids," *PNAS* 109(40): 16101-16106 (2012)).

[0233] In some instances, the polynucleic acid molecule is conjugated to the binding moiety by a site-directed method utilizing an enzyme-catalyzed process. In some instances, the site-directed method utilizes SMARTag™ technology (Catalent, Inc.). In some instances, the SMARTag™ technology comprises generation of a formylglycine (FGly) residue from cysteine by formylglycine-generating enzyme (FGE) through an oxidation process under the presence of an aldehyde tag and the subsequent conjugation of FGly to an alkylhydrazine-functionalized polynucleic acid molecule via hydrazino-Pictet-Spengler (HIPS) ligation. (see Wu et al., "Site-specific chemical modification of recombinant proteins produced in mammalian cells by using the genetically encoded aldehyde tag," *PNAS* 106(9): 3000-3005 (2009); Agarwal, et al., "A Pictet-Spengler ligation for protein chemical modification," *PNAS* 110(1): 46-51 (2013))

[0234] In some instances, the enzyme-catalyzed process comprises microbial transglutaminase (mTG). In some cases, the polynucleic acid molecule is conjugated to the binding moiety utilizing a microbial transglutaminase-catalyzed process. In some instances, mTG catalyzes the formation of a covalent bond between the amide side chain of a glutamine within the recognition sequence and a primary amine of a functionalized polynucleic acid molecule. In some instances, mTG is produced from *Streptomyces mobarensis*. (see Strop et al., "Location matters: site of conjugation modulates stability and pharmacokinetics of antibody drug conjugates," *Chemistry and Biology* 20(2) 161-167 (2013))

[0235] In some instances, the polynucleic acid molecule is conjugated to the binding moiety by a method as described in PCT Publication No. WO2014/140317, which utilizes a sequence-specific transpeptidase.

[0236] In some instances, the polynucleic acid molecule is conjugated to the binding moiety by a method as described in U.S. Patent Publication Nos. 2015/0105539 and 2015/0105540.

Polymer Conjugating Moiety

[0237] In some embodiments, a polymer moiety C is further conjugated to a polynucleic acid molecule described herein, a binding moiety described herein, or in combinations thereof. In some instances, a polymer moiety C is conjugated a polynucleic acid molecule in a formula A-X₁-B-X₂-C (X₁, X₂ as two linkers conjugating A and B, B and C, respectively). In some cases, a polymer moiety C is conjugated to a binding moiety. In other cases, a polymer moiety C is conjugated to a polynucleic acid molecule-binding moiety molecule. In additional cases, a polymer moiety C is conjugated, as illustrated supra.

[0238] In some instances, the polymer moiety C is a natural or synthetic polymer, consisting of long chains of branched or unbranched monomers, and/or cross-linked network of monomers in two or three dimensions. In some

instances, the polymer moiety C includes a polysaccharide, lignin, rubber, or polyalkylene oxide (e.g., polyethylene glycol). In some instances, the at least one polymer moiety C includes, but is not limited to, alpha-, omega-dihydroxypolyethyleneglycol, biodegradable lactone-based polymer, e.g. polyacrylic acid, polylactide acid (PLA), poly(glycolic acid) (PGA), polypropylene, polystyrene, polyolefin, polyamide, polycyanoacrylate, polyimide, polyethylene terephthalate (also known as poly(ethylene terephthalate), PET, PETG, or PETE), polytetramethylene glycol (PTG), or polyurethane as well as mixtures thereof. As used herein, a mixture refers to the use of different polymers within the same compound as well as in reference to block copolymers. In some cases, block copolymers are polymers wherein at least one section of a polymer is build up from monomers of another polymer. In some instances, the polymer moiety C comprises polyalkylene oxide. In some instances, the polymer moiety C comprises PEG. In some instances, the polymer moiety C comprises polyethylene imide (PEI) or hydroxy ethyl starch (HES).

[0239] In some instances, C is a PEG moiety. In some instances, the PEG moiety is conjugated at the 5' terminus of the polynucleic acid molecule while the binding moiety is conjugated at the 3' terminus of the polynucleic acid molecule. In some instances, the PEG moiety is conjugated at the 3' terminus of the polynucleic acid molecule while the binding moiety is conjugated at the 5' terminus of the polynucleic acid molecule. In some instances, the PEG moiety is conjugated to an internal site of the polynucleic acid molecule. In some instances, the PEG moiety, the binding moiety, or a combination thereof, are conjugated to an internal site of the polynucleic acid molecule. In some instances, the conjugation is a direct conjugation. In some instances, the conjugation is via native ligation.

[0240] In some embodiments, the polyalkylene oxide (e.g., PEG) is a polydisperse or monodisperse compound. In some instances, polydisperse material comprises disperse distribution of different molecular weight of the material, characterized by mean weight (weight average) size and dispersity. In some instances, the monodisperse PEG comprises one size of molecules. In some embodiments, C is poly- or monodispersed polyalkylene oxide (e.g., PEG) and the indicated molecular weight represents an average of the molecular weight of the polyalkylene oxide, e.g., PEG, molecules.

[0241] In some embodiments, the molecular weight of the polyalkylene oxide (e.g. PEG) is about 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1450, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3250, 3350, 3500, 3750, 4000, 4250, 4500, 4600, 4750, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 10,000, 12,000, 20,000, 35,000, 40,000, 50,000, 60,000, or 100,000 Da.

[0242] In some embodiments, C is polyalkylene oxide (e.g., PEG) and has a molecular weight of about 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1450, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3250, 3350, 3500, 3750, 4000, 4250, 4500, 4600, 4750, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 10,000, 12,000, 20,000, 35,000, 40,000, 50,000, 60,000, or 100,000 Da. In some embodiments, C is PEG and has a molecular weight of about 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1450, 1500, 1600, 1700, 1800, 1900,

2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3250, 3350, 3500, 3750, 4000, 4250, 4500, 4600, 4750, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 10,000, 12,000, 20,000, 35,000, 40,000, 50,000, 60,000, or 100,000 Da. In some instances, the molecular weight of C is about 200 Da. In some instances, the molecular weight of C is about 300 Da. In some instances, the molecular weight of C is about 400 Da. In some instances, the molecular weight of C is about 500 Da. In some instances, the molecular weight of C is about 600 Da. In some instances, the molecular weight of C is about 700 Da. In some instances, the molecular weight of C is about 800 Da. In some instances, the molecular weight of C is about 900 Da. In some instances, the molecular weight of C is about 1000 Da. In some instances, the molecular weight of C is about 1100 Da. In some instances, the molecular weight of C is about 1200 Da. In some instances, the molecular weight of C is about 1300 Da. In some instances, the molecular weight of C is about 1400 Da. In some instances, the molecular weight of C is about 1450 Da. In some instances, the molecular weight of C is about 1500 Da. In some instances, the molecular weight of C is about 1600 Da. In some instances, the molecular weight of C is about 1700 Da. In some instances, the molecular weight of C is about 1800 Da. In some instances, the molecular weight of C is about 1900 Da. In some instances, the molecular weight of C is about 2000 Da. In some instances, the molecular weight of C is about 2100 Da. In some instances, the molecular weight of C is about 2200 Da. In some instances, the molecular weight of C is about 2300 Da. In some instances, the molecular weight of C is about 2400 Da. In some instances, the molecular weight of C is about 2500 Da. In some instances, the molecular weight of C is about 2600 Da. In some instances, the molecular weight of C is about 2700 Da. In some instances, the molecular weight of C is about 2800 Da. In some instances, the molecular weight of C is about 2900 Da. In some instances, the molecular weight of C is about 3000 Da. In some instances, the molecular weight of C is about 3250 Da. In some instances, the molecular weight of C is about 3350 Da. In some instances, the molecular weight of C is about 3500 Da. In some instances, the molecular weight of C is about 3750 Da. In some instances, the molecular weight of C is about 4000 Da. In some instances, the molecular weight of C is about 4250 Da. In some instances, the molecular weight of C is about 4500 Da. In some instances, the molecular weight of C is about 4600 Da. In some instances, the molecular weight of C is about 4750 Da. In some instances, the molecular weight of C is about 5000 Da. In some instances, the molecular weight of C is about 5500 Da. In some instances, the molecular weight of C is about 6000 Da. In some instances, the molecular weight of C is about 6500 Da. In some instances, the molecular weight of C is about 7000 Da. In some instances, the molecular weight of C is about 7500 Da. In some instances, the molecular weight of C is about 8000 Da. In some instances, the molecular weight of C is about 10,000 Da. In some instances, the molecular weight of C is about 12,000 Da. In some instances, the molecular weight of C is about 20,000 Da. In some instances, the molecular weight of C is about 35,000 Da. In some instances, the molecular weight of C is about 40,000 Da. In some instances, the molecular weight of C is about 50,000 Da. In some instances, the molecular weight of C is about 60,000 Da. In some instances, the molecular weight of C is about 100,000 Da.

[0248] wherein m is independently at each occurrence 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, preferably 4-6 or 5; and n is independently at each occurrence 1, 2, 3, 4, or 5. In some embodiments, m and n are, for example, about 10.

[0249] In some instances, cMAP is further conjugated to a PEG moiety, generating a cMAP-PEG copolymer, an mPEG-cMAP-PEGm triblock polymer, or a cMAP-PEG-cMAP triblock polymer. In some instances, the PEG moiety is in a range of from about 500 Da to about 50,000 Da. In some instances, the PEG moiety is in a range of from about 500 Da to about 1000 Da, greater than 1000 Da to about 5000 Da, greater than 5000 Da to about 10,000 Da, greater than 10,000 to about 25,000 Da, greater than 25,000 Da to about 50,000 Da, or any combination of two or more of these ranges.

[0250] In some instances, the polymer moiety C is cMAP-PEG copolymer, an mPEG-cMAP-PEGm triblock polymer, or a cMAP-PEG-cMAP triblock polymer. In some cases, the polymer moiety C is cMAP-PEG copolymer. In other cases, the polymer moiety C is an mPEG-cMAP-PEGm triblock polymer. In additional cases, the polymer moiety C is a cMAP-PEG-cMAP triblock polymer.

[0251] In some embodiments, the polymer moiety C is conjugated to the polynucleic acid molecule, the binding moiety, and optionally to the endosomolytic moiety as illustrated supra.

Endosomolytic or Cell Membrane Penetration Moiety

[0252] In some embodiments, a molecule of Formula (I): A-X₁-B-X₂-C, further comprises an additional conjugating moiety. In some instances, the additional conjugating moiety is an endosomolytic moiety and/or a cell membrane penetration moiety. In some cases, the endosomolytic moiety is a cellular compartmental release component, such as a compound capable of releasing from any of the cellular compartments known in the art, such as the endosome, lysosome, endoplasmic reticulum (ER), Golgi apparatus, microtubule, peroxisome, or other vesicular bodies with the cell. In some cases, the endosomolytic moiety comprises an endosomolytic polypeptide, an endosomolytic polymer, an endosomolytic lipid, or an endosomolytic small molecule. In some cases, the endosomolytic moiety comprises an endosomolytic polypeptide. In other cases, the endosomolytic moiety comprises an endosomolytic polymer. In some cases, the cell membrane penetration moiety comprises a cell penetrating peptide (CPP). In other cases, the cell membrane penetration moiety comprises a cell penetrating lipid. In other cases, the cell membrane penetration moiety comprises a cell penetrating small molecule.

Endosomolytic and Cell Membrane Penetration Polypeptides

[0253] In some embodiments, a molecule of Formula (I): A-X₁-B-X₂-C, is further conjugated with an endosomolytic polypeptide. In some cases, the endosomolytic polypeptide is a pH-dependent membrane active peptide. In some cases, the endosomolytic polypeptide is an amphipathic polypeptide. In additional cases, the endosomolytic polypeptide is a peptidomimetic. In some instances, the endosomolytic polypeptide comprises INF, melittin, meucin, or their respective derivatives thereof. In some instances, the endosomolytic polypeptide comprises INF or its derivatives thereof. In other cases, the endosomolytic polypeptide comprises melit-

tin or its derivatives thereof. In additional cases, the endosomolytic polypeptide comprises meucin or its derivatives thereof.

[0254] In some instances, INF7 is a 24 residue polypeptide those sequence comprises CGIFGEIEELIEEGLEN-LIDWGNA (SEQ ID NO: 331), or GLFEAIEGFIENGWEGMIDGWYGC (SEQ ID NO: 332). In some instances, INF7 or its derivatives comprise a sequence of: GLFEAIEGFIENGWEGMIWDYGSWSCG (SEQ ID NO: 333), GLFEAIEGFIENGWEGMIDG WYG-(PEG)6-NH₂ (SEQ ID NO: 334), or GLFEAIEGFIENGWEGMIWDYGSWSC-K(GalNAc)₂ (SEQ ID NO: 335).

[0255] In some cases, melittin is a 26 residue polypeptide those sequence comprises CLIGAILKV-LATGLPTLISWIKNKRKQ (SEQ ID NO. 336), or GIGAVLKVLTGLPALISWIKRKRQQ (SEQ ID NO: 337) In some instances, melittin comprises a polypeptide sequence as described in U.S. Pat. No. 8,501,930.

[0256] In some instances, meucin is an antimicrobial peptide (AMP) derived from the venom gland of the scorpion *Mesobuthus eupeus*. In some instances, meucin comprises of meucin-13 those sequence comprises IFGA-IAGLLKNIF-NH₂ (SEQ ID NO: 338) and meucin-18 those sequence comprises FFGHLFKLATKIIPSLFQ (SEQ ID NO: 339).

[0257] In some instances, the endosomolytic polypeptide comprises a polypeptide in which its sequence is at least 50%, 60%, 70%, 80%, 90%, 95%, or 99% sequence identity to INF7 or its derivatives thereof, melittin or its derivatives thereof, or meucin or its derivatives thereof. In some instances, the endosomolytic moiety comprises INF7 or its derivatives thereof, melittin or its derivatives thereof, or meucin or its derivatives thereof.

[0258] In some instances, the endosomolytic moiety is INF7 or its derivatives thereof. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOS: 331-335. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 331. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 332-335. In some cases, the endosomolytic moiety comprises SEQ ID NO: 331. In some cases, the endosomolytic moiety comprises SEQ ID NO: 332-335. In some cases, the endosomolytic moiety consists of SEQ ID NO: 331. In some cases, the endosomolytic moiety consists of SEQ ID NO: 332-335.

[0259] In some instances, the endosomolytic moiety is melittin or its derivatives thereof. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOS: 336 or 337. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 336. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 337. In some cases, the

endosomolytic moiety comprises SEQ ID NO: 286. In some cases, the endosomolytic moiety comprises SEQ ID NO: 337. In some cases, the endosomolytic moiety consists of SEQ ID NO: 336. In some cases, the endosomolytic moiety consists of SEQ ID NO: 337.

[0260] In some instances, the endosomolytic moiety is meucin or its derivatives thereof. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NOs: 338 or 339. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%,

65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 338. In some cases, the endosomolytic moiety comprises a polypeptide having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 339. In some cases, the endosomolytic moiety comprises SEQ ID NO: 338. In some cases, the endosomolytic moiety comprises SEQ ID NO: 339. In some cases, the endosomolytic moiety consists of SEQ ID NO: 338. In some cases, the endosomolytic moiety consists of SEQ ID NO: 339.

[0261] In some instances, the endosomolytic moiety comprises a sequence as illustrated in Table 8

TABLE 8

NAME	ORIGIN	AMINO ACID SEQUENCE	SEQ ID NO:	TYPE
Pep-1	NLS from Simian Virus 40 large antigen and Reverse transcriptase of HIV	KETWWETWWTEWSQPKKKRKV	340	Primary amphipathic
pVEC	VE-cadherin	LLIILRRRRIRKQAHASK	341	Primary amphipathic
VT5	Synthetic peptide	DPKGDPKGVTVTVTVTVTGKGDPKPD	342	β -sheet amphipathic
C105Y	1-antitrypsin	CSIPPEVKFNKPFVYLI	343	—
Transportan	Galanin and mastoparan	GWTLNSAGYLLGKINLKALAALAKKIL	344	Primary amphipathic
TP10	Galanin and mastoparan	AGYLLGKINLKALAALAKKIL	345	Primary amphipathic
MPG	A hydrophobic domain from the fusion sequence of HIV gp41 and NLS of SV40 T antigen	GALFLGFLGAAGSTMGA	346	β -sheet amphipathic
gH625	Glycoprotein gH of HSV type I	HGLASTLTRWAHYNALIRAF	347	Secondary amphipathic α -helical
CADY	PPTG1 peptide	GLWRALWRLLRSLWRLLWRA	348	Secondary amphipathic α -helical
GALA	Synthetic peptide	WEAALAEALAEALAEHLAEALAE ALEALAA	349	Secondary amphipathic α -helical
INF	Influenza HA2 fusion peptide	GLFEAIEGFIENGWEGMIDGWYGC	350	Secondary amphipathic α -helical/pH-dependent membrane active peptide
HA2E5-TAT	Influenza HA2 subunit of influenza virus X31 strain fusion peptide	GLFGAIAGFIENGWEGMIDGWYG	351	Secondary amphipathic α -helical/pH-dependent membrane active peptide

ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino) quinoline; 4-(4-ethyl-(2-hydroxy-ethyl)-amino-1-methylbutylamino)-quinoline; 7-hydroxy-4-(4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline; hydroxychloroquine phosphate; 7-chloro-4-(4-ethyl-(2-hydroxyethyl-1)-amino-1-butylamino)quinoline (desmethyl-hydroxychloroquine); 7-fluoro-4-(4-ethyl-(2-hydroxy-ethyl)-amino-1-butylamino)quinoline; 4-(4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline; 7-hydroxy-4-(4-ethyl-(2-hydroxyethyl)-amino-1-butylamino) quinoline; 7-chloro-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline; 7-fluoro-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline;

keto, sulfhydryl and vinyl derivatives or analogs thereof. In some instances, an endosomolytic moiety is a small molecule described in Naisbitt et al (1997, J Pharmacol Exp Therapy 280:884-893) and in U.S. Pat. No. 5,736,557.

Cell Penetrating Polypeptide (CPP)

[0267] In some embodiments, cell penetrating polypeptide comprises positively charged short peptides with 5-30 amino acids. In some embodiments, cell penetrating polypeptide comprises arginine or lysine rich amino acid sequences. In some embodiments, cell penetrating polypeptide includes any polypeptide or combination thereof listed in Table 9

TABLE 9

Peptide	Sequence	SEQ ID NO
Antennapedia Penetratin (43-58)	RQIKIWFQNRRMKWKK	358
HIV-1 TAT protein (48-60)	GRKKRRQRRRPPQ	359
pVEC Cadherin (615-632)	LLIILRRRIRKQAHASK	360
Transportan Galanine/Mastoparan	GWTLNSAGYLLGKINLKALAALAKKIL	361
MPG HIV-gp41/SV40 T-antigen	GALFLGFLGAAGSTMGAWSQPKKKRKV	362
Pep-1 HIV-reverse transcriptase/SV40 T-antigen	KETWWETWTEWSQPKKKRKV	363
Polyarginines	R(n); 6 < n < 12	364
MAP	KLALKLALKALKALKLA	365
R6W3	RRWRRWRR	366
NLS	CGYGPKKKKRKG	367
8-lysines	KKKKKKKK	368
ARF (1-22)	MVRRFLVTLRIRACGPPRRV	369
Azurin-p28	LSTAADMQGVVTDGMASGLDKDYLPDD	370

4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline; 7-hydroxy-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-butylamino)quinoline; 7-chloro-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline; 7-fluoro-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino) quinoline; 4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino)quinoline; 7-hydroxy-4-(1-carboxy-4-ethyl-(2-hydroxyethyl)-amino-1-methylbutylamino) quinoline; 8-[(4-aminopentyl)amino]-6-methoxydihydrochloride quinoline; 1-acetyl-1,2,3,4-tetrahydroquinoline; 8-[(4-aminopentyl)amino]-6-methoxyquinoline dihydrochloride; 1-butyryl-1,2,3,4-tetrahydroquinoline; 3-chloro-4-(4-hydroxy-alpha, alpha'-bis(2-methyl-1-pyrrolidinyl)-2,5-xylidinoquinoline, 4-[(4-diethyl-amino)-1-methylbutyl-amino]-6-methoxyquinoline; 3-fluoro-4-(4-hydroxy-alpha, alpha'-bis(2-methyl-1-pyrrolidinyl)-2,5-xylidinoquinoline, 4-[(4-diethylamino)-1-methylbutyl-amino]-6-methoxyquinoline; 4-(4-hydroxy-alpha, alpha'-bis(2-methyl-1-pyrrolidinyl)-2,5-xylidinoquinoline; 4-[(4-diethylamino)-1-methylbutyl-amino]-6-methoxyquinoline; 3,4-dihydro-1-(2H)-quinolinecarboxyaldehyde; 1,1'-pentamethylene diquinoleinium diiodide; 8-quinolinol sulfate and amino, aldehyde, carboxylic, hydroxyl, halogen,

Linkers

[0268] In some embodiments, a linker described herein is a cleavable linker or a non-cleavable linker. In some instances, the linker is a cleavable linker. In other instances, the linker is a non-cleavable linker.

[0269] In some cases, the linker is a non-polymeric linker. A non-polymeric linker refers to a linker that does not contain a repeating unit of monomers generated by a polymerization process. Exemplary non-polymeric linkers include, but are not limited to, C₁-C₆ alkyl group (e.g., a C₅, C₄, C₃, C₂, or C₁ alkyl group), homobifunctional cross linkers, heterobifunctional cross linkers, peptide linkers, traceless linkers, self-immolative linkers, maleimide-based linkers, or combinations thereof. In some cases, the non-polymeric linker comprises a C₁-C₆ alkyl group (e.g. a C₅, C₄, C₃, C₂, or C₁ alkyl group), a homobifunctional cross linker, a heterobifunctional cross linker, a peptide linker, a traceless linker, a self-immolative linker, a maleimide-based linker, or a combination thereof. In additional cases, the non-polymeric linker does not comprise more than two of the same type of linkers, e.g., more than two homobifunctional cross linkers, or more than two peptide linkers. In further cases, the non-polymeric linker optionally comprises one or more reactive functional groups.

[0270] In some instances, the non-polymeric linker does not encompass a polymer that is described above. In some instances, the non-polymeric linker does not encompass a polymer encompassed by the polymer moiety C. In some cases, the non-polymeric linker does not encompass a polyalkylene oxide (e.g., PEG). In some cases, the non-polymeric linker does not encompass a PEG.

[0271] In some instances, the linker comprises a homobifunctional linker. Exemplary homobifunctional linkers include, but are not limited to, Lomant's reagent dithiobis(succinimidylpropionate) DSP, 3'3'-dithiobis(sulfosuccinimidyl propionate) (DTSSP), disuccinimidyl suberate (DSS), bis(sulfosuccinimidyl)suberate (BS), disuccinimidyl tartrate (DST), disulfosuccinimidyl tartrate (sulfo DST), ethylene glycobis(succinimidylsuccinate) (EGS), disuccinimidyl glutarate (DSG), N,N'-disuccinimidyl carbonate (DSC), dimethyl adipimidate (DMA), dimethyl pimelimidate (DMP), dimethyl suberimidate (DMS), dimethyl-3,3'-dithiobispropionimidate (DTBP), 1,4-di-3'-(2'-pyridyl)dithio)propionamido)butane (DPDPB), bismaleimidohexane (BMH), aryl halide-containing compound (DFDNB), such as e.g. 1,5-difluoro-2,4-dinitrobenzene or 1,3-difluoro-4,6-dinitrobenzene, 4,4'-difluoro-3,3'-dinitrophenylsulfone (DFDNPS), bis- $[\beta$ -(4-azidosalicylamido)ethyl]disulfide (BASED), formaldehyde, glutaraldehyde, 1,4-butanediol diglycidyl ether, adipic acid dihydrazide, carbonyldiimidazole, o-toluidine, 3,3'-dimethylbenzidine, benzidine, α,α' -p-diaminodiphenyl, diiodo-p-xylene sulfonic acid, N,N'-ethylene-bis(iodoacetamide), or N,N'-hexamethylene-bis(iodoacetamide).

[0272] In some embodiments, the linker comprises a heterobifunctional linker. Exemplary heterobifunctional linker include, but are not limited to, amine-reactive and sulfhydryl cross-linkers such as N-succinimidyl 3-(2-pyridyl)dithio)propionate (sPDP), long-chain N-succinimidyl 3-(2-pyridyl)dithio)propionate (LC-sPDP), water-soluble-long-chain N-succinimidyl 3-(2-pyridyl)dithio)propionate (sulfo-LC-sPDP), succinimidylloxycarbonyl- α -methyl- α -(2-pyridyl)dithio)toluene (sMPT), sulfosuccinimidyl-6-[α -methyl- α -(2-pyridyl)dithio)toluamido]hexanoate (sulfo-LC-sMPT), succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sMCC), sulfosuccinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-sMCC), m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBs), m-maleimidobenzoyl-N-hydroxysulfosuccinimide ester (sulfo-MBs), N-succinimidyl(4-iodoacteyl)aminobenzoate (sIAB), sulfosuccinimidyl(4-iodoacteyl)aminobenzoate (sulfo-sIAB), succinimidyl-4-(p-maleimidophenyl)butyrate (sMPB), sulfosuccinimidyl-4-(p-maleimidophenyl)butyrate (sulfo-sMPB), N-(γ -maleimidobutyryloxy)succinimide ester (GMBs), N-(γ -maleimidobutyryloxy)sulfosuccinimide ester (sulfo-GMBs), succinimidyl 6-((iodoacetyl)amino)hexanoate (sIAX), succinimidyl 6-[6-(((iodoacetyl)amino)hexanoyl)amino]hexanoate (sIAXX), succinimidyl 4-(((iodoacetyl)amino)methyl)cyclohexane-1-carboxylate (sIAC), succinimidyl 6-(((4-iodoacetyl)amino)methyl)cyclohexane-1-carboxylate (sIACX), p-nitrophenyl iodoacetate (NPIA), carbonyl-reactive and sulfhydryl-reactive cross-linkers such as 4-(4-N-maleimidophenyl)butyric acid hydrazide (MPBH), 4-(N-maleimidomethyl)cyclohexane-1-carboxyl-hydrazide-8 (M_2C_2H), 3-(2-pyridyl)dithio)propionyl hydrazide (PDPH), amine-reactive and photoreactive cross-linkers such as N-hydroxysuccinimidyl-4-azidosalicylic acid (NHs-AsA), N-hydroxysulfosuccinimidyl-4-azidosalicylic acid (sulfo-NHs-AsA), sulfos-

uccinimidyl-(4-azidosalicylamido)hexanoate (sulfo-NHs-LC-AsA), sulfosuccinimidyl-2-(ρ -azidosalicylamido)ethyl-1,3'-dithiopropanoate (sAsD), N-hydroxysuccinimidyl-4-azidobenzoate (HsAB), N-hydroxysulfosuccinimidyl-4-azidobenzoate (sulfo-HsAB), N-succinimidyl-6-(4'-azido-2'-nitrophenylamino)hexanoate (sANPAH), sulfosuccinimidyl-6-(4'-azido-2'-nitrophenylamino)hexanoate (sulfo-sANPAH), N-5-azido-2-nitrobenzoyloxysuccinimide (ANB-NOs), sulfosuccinimidyl-2-(m-azido-o-nitrobenzamido)-ethyl-1,3'-dithiopropanoate (sAND), N-succinimidyl-4(4-azidophenyl)1,3'-dithiopropanoate (sADP), N-sulfosuccinimidyl(4-azidophenyl)-1,3'-dithiopropanoate (sulfo-sADP), sulfosuccinimidyl 4-(p-azidophenyl)butyrate (sulfo-sAPB), sulfosuccinimidyl 2-(7-azido-4-methylcoumarin-3-acetamide)ethyl-1,3'-dithiopropanoate (sAED), sulfosuccinimidyl 7-azido-4-methylcoumarin-3-acetate (sulfo-sAMCA), ρ -nitrophenyl diazopyruvate (ρ NPDP), ρ -nitrophenyl-2-diazo-3,3,3-trifluoropropionate (PNP-DTP), sulfhydryl-reactive and photoreactive cross-linkers such as 1-(ρ -Azidosalicylamido)-4-(iodoacetamido)butane (AsIB), N-[4-(ρ -azidosalicylamido)butyl]-3'-(2'-pyridyl)dithio)propionamide (APDP), benzophenone-4-iodoacetamide, benzophenone-4-maleimide carbonyl-reactive and photoreactive cross-linkers such as ρ -azidobenzoyl hydrazide (ABH), carboxylate-reactive and photoreactive cross-linkers such as 4-(ρ -azidosalicylamido)butylamine (AsBA), and arginine-reactive and photoreactive cross-linkers such as ρ -azidophenyl glyoxal (APG).

[0273] In some instances, the linker comprises a reactive functional group. In some cases, the reactive functional group comprises a nucleophilic group that is reactive to an electrophilic group present on a binding moiety. Exemplary electrophilic groups include carbonyl groups-such as aldehyde, ketone, carboxylic acid, ester, amide, enone, acyl halide or acid anhydride. In some embodiments, the reactive functional group is aldehyde. Exemplary nucleophilic groups include hydrazide, oxime, amino, hydrazine, thiosemicarbazone, hydrazine carboxylate, and arylhydrazide.

[0274] In some embodiments, the linker comprises a maleimide group. In some instances, the maleimide group is also referred to as a maleimide spacer. In some instances, the maleimide group further encompasses a caproic acid, forming maleimidocaproyl (mc). In some cases, the linker comprises maleimidocaproyl (mc). In some cases, the linker is maleimidocaproyl (mc). In other instances, the maleimide group comprises a maleimidomethyl group, such as succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sMCC) or sulfosuccinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-sMCC) described above.

[0275] In some embodiments, the maleimide group is a self-stabilizing maleimide. In some instances, the self-stabilizing maleimide utilizes diaminopropionic acid (DPR) to incorporate a basic amino group adjacent to the maleimide to provide intramolecular catalysis of tiosuccinimide ring hydrolysis, thereby eliminating maleimide from undergoing an elimination reaction through a retro-Michael reaction. In some instances, the self-stabilizing maleimide is a maleimide group described in Lyon et al., "Self-hydrolyzing maleimides improve the stability and pharmacological properties of antibody-drug conjugates," Nat. Biotechnol. 32(10): 1059-1062 (2014). In some instances, the linker comprises a self-stabilizing maleimide. In some instances, the linker is a self-stabilizing maleimide.

[0276] In some embodiments, the linker comprises a peptide moiety. In some instances, the peptide moiety comprises at least 2, 3, 4, 5, or 6 more amino acid residues. In some instances, the peptide moiety comprises at most 2, 3, 4, 5, 6, 7, or 8 amino acid residues. In some instances, the peptide moiety comprises about 2, about 3, about 4, about 5, or about 6 amino acid residues. In some instances, the peptide moiety is a cleavable peptide moiety (e.g., either enzymatically or chemically). In some instances, the peptide moiety is a non-cleavable peptide moiety. In some instances, the peptide moiety comprises Val-Cit (valine-citrulline). Gly-Gly-Phe-Gly (SEQ ID NO: 403), Phe-Lys, Val-Lys, Gly-Phe-Lys, Phe-Phe-Lys, Ala-Lys, Val-Arg, Phe-Cit, Phe-Arg, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Ala, Ala-Leu-Ala-Leu (SEQ ID NO: 404), or Gly-Phe-Leu-Gly (SEQ ID NO: 410). In some instances, the linker comprises a peptide moiety such as: Val-Cit (valine-citrulline), Gly-Gly-Phe-Gly, Phe-Lys, Val-Lys, Gly-Phe-Lys, Phe-Phe-Lys, Ala-Lys, Val-Arg, Phe-Cit, Phe-Arg, Leu-Cit, Ile-Cit, Trp-Cit, Phe-Ala, Ala-Leu-Ala-Leu, or Gly-Phe-Leu-Gly (SEQ ID NO: 405). In some cases, the linker comprises Val-Cit. In some cases, the linker is Val-Cit.

[0277] In some embodiments, the linker comprises a benzoic acid group, or its derivatives thereof. In some instances, the benzoic acid group or its derivatives thereof comprise paraaminobenzoic acid (PABA). In some instances, the benzoic acid group or its derivatives thereof comprise gamma-aminobutyric acid (GABA).

[0278] In some embodiments, the linker comprises one or more of a maleimide group, a peptide moiety, and/or a benzoic acid group, in any combination. In some embodiments, the linker comprises a combination of a maleimide group, a peptide moiety, and/or a benzoic acid group. In some instances, the maleimide group is maleimidocaproyl (mc). In some instances, the peptide group is val-cit. In some instances, the benzoic acid group is PABA. In some instances, the linker comprises a mc-val-cit group. In some cases, the linker comprises a val-cit-PABA group. In additional cases, the linker comprises a mc-val-cit-PABA group.

[0279] In some embodiments, the linker is a self-immolative linker or a self-elimination linker. In some cases, the linker is a self-immolative linker. In other cases, the linker is a self-elimination linker (e.g., a cyclization self-elimination linker). In some instances, the linker comprises a linker described in U.S. Pat. No. 9,089,614 or PCT Publication NO. WO2015038426.

[0280] In some embodiments, the linker is a dendritic type linker. In some instances, the dendritic type linker comprises a branching, multifunctional linker moiety. In some instances, the dendritic type linker is used to increase the molar ratio of polynucleotide B to the binding moiety A. In some instances, the dendritic type linker comprises PAMAM dendrimers.

[0281] In some embodiments, the linker is a traceless linker or a linker in which after cleavage does not leave behind a linker moiety (e.g., an atom or a linker group) to a binding moiety A, a polynucleotide B, a polymer C, or an endosomolytic moiety D. Exemplary traceless linkers include, but are not limited to, germanium linkers, silicium linkers, sulfur linkers, selenium linkers, nitrogen linkers, phosphorus linkers, boron linkers, chromium linkers, or phenylhydrazide linker. In some cases, the linker is a traceless aryl-triazene linker as described in Hejesen, et al., "A traceless aryl-triazene linker for DNA-directed chemistry."

Org Biomol Chem 11(15): 2493-2497 (2013). In some instances, the linker is a traceless linker described in Blaney, et al., "Traceless solid-phase organic synthesis," *Chem. Rev.* 102: 2607-2024 (2002). In some instances, a linker is a traceless linker as described in U.S. Pat. No. 6,821,783.

[0282] In some instances, the linker is a linker described in U.S. Pat. Nos. 6,884,869; 7,498,298; 8,288,352; 8,609,105; or 8,697,688; U.S. Patent Publication NOs. 2014/0127239; 2013/028919; 2014/286970; 2013/0309256; 2015/037360; or 2014/0294851; or PCT Publication NOs. WO2015057699; WO2014080251; WO2014197854; WO2014145090; or WO2014177042.

[0283] In some embodiments, X_1 and X_2 are each independently a bond or a non-polymeric linker. In some instances, X_1 and X_2 are each independently a bond. In some cases, X_1 and X_2 are each independently a non-polymeric linker.

[0284] In some instances, X_1 is a bond or a non-polymeric linker. In some instances, X_1 is a bond. In some instances, X_1 is a non-polymeric linker. In some instances, the linker is a C_1 - C_6 alkyl group. In some cases, X_1 is a C_1 - C_6 alkyl group, such as for example, a C_5 , C_4 , C_3 , C_2 , or C_1 alkyl group. In some cases, the C_1 - C_6 alkyl group is an unsubstituted C_1 - C_6 alkyl group. As used in the context of a linker, and in particular in the context of X_1 , alkyl means a saturated straight or branched hydrocarbon radical containing up to six carbon atoms. In some instances, X_1 includes a homobifunctional linker or a heterobifunctional linker described supra. In some cases, X_1 includes a heterobifunctional linker. In some cases, X_1 includes sMCC. In other instances, X_1 includes a heterobifunctional linker optionally conjugated to a C_1 - C_6 alkyl group. In other instances, X_1 includes sMCC optionally conjugated to a C_1 - C_6 alkyl group. In additional instances, X_1 does not include a homobifunctional linker or a heterobifunctional linker described supra.

[0285] In some instances, X_2 is a bond or a linker. In some instances, X_2 is a bond. In other cases, X_2 is a linker. In additional cases, X_2 is a non-polymeric linker. In some embodiments, X_2 is a C_1 - C_6 alkyl group. In some instances, X_2 is a homobifunctional linker or a heterobifunctional linker described supra. In some instances, X_2 is a homobifunctional linker described supra. In some instances, X_2 is a heterobifunctional linker described supra. In some instances, X_2 comprises a maleimide group, such as maleimidocaproyl (mc) or a self-stabilizing maleimide group described above. In some instances, X_2 comprises a peptide moiety, such as Val-Cit. In some instances, X_2 comprises a benzoic acid group, such as PABA. In additional instances, X_2 comprises a combination of a maleimide group, a peptide moiety, and/or a benzoic acid group. In additional instances, X_2 comprises a mc group. In additional instances, X_2 comprises a mc-val-cit group. In additional instances, X_2 comprises a val-cit-PABA group. In additional instances, X_2 comprises a mc-val-cit-PABA group.

Methods of Use

[0286] Muscle atrophy refers to a loss of muscle mass and/or to a progressive weakening and degeneration of muscles. In some cases, the loss of muscle mass and/or the progressive weakening and degeneration of muscles occurs due to a high rate of protein degradation, a low rate of protein synthesis, or a combination of both. In some cases, a high rate of muscle protein degradation is due to muscle

protein catabolism (i.e., the breakdown of muscle protein in order to use amino acids as substrates for gluconeogenesis).

[0287] In one embodiment, muscle atrophy refers to a significant loss in muscle strength. By significant loss in muscle strength is meant a reduction of strength in diseased, injured, or unused muscle tissue in a subject relative to the same muscle tissue in a control subject. In an embodiment, a significant loss in muscle strength is a reduction in strength of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or more relative to the same muscle tissue in a control subject. In another embodiment, by significant loss in muscle strength is meant a reduction of strength in unused muscle tissue relative to the muscle strength of the same muscle tissue in the same subject prior to a period of nonuse. In an embodiment, a significant loss in muscle strength is a reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or more relative to the muscle strength of the same muscle tissue in the same subject prior to a period of nonuse.

[0288] In another embodiment, muscle atrophy refers to a significant loss in muscle mass. By significant loss in muscle mass is meant a reduction of muscle volume in diseased, injured, or unused muscle tissue in a subject relative to the same muscle tissue in a control subject. In an embodiment, a significant loss of muscle volume is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or more relative to the same muscle tissue in a control subject. In another embodiment, by significant loss in muscle mass is meant a reduction of muscle volume in unused muscle tissue relative to the muscle volume of the same muscle tissue in the same subject prior to a period of nonuse. In an embodiment, a significant loss in muscle tissue is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or more relative to the muscle volume of the same muscle tissue in the same subject prior to a period of nonuse. Muscle volume is optionally measured by evaluating the cross-section area of a muscle such as by Magnetic Resonance Imaging (e.g. by a muscle volume/cross-section area (CSA) MRI method).

[0289] In some embodiments, described herein is a method of treating muscle atrophy in a subject, which comprises providing polynucleic acid molecule described herein and administering to the subject a therapeutically effective amount of a polynucleic acid molecule described herein or a polynucleic acid molecule conjugate described herein to reduce a quantity of the mRNA transcript of human DUX4. In some instances, the muscle atrophy is associated with Facioscapulohumeral muscular dystrophy (FSHD). The polynucleic acid moiety mediates RNA interference against the human DUX4 as to modulating muscle atrophy in a subject. In some embodiments, expression of one or more marker genes that are affected by DUX4 expression is also altered or modulated (e.g., decreased) by the decreased expression of human DUX4. The marker genes includes, but not limited to, MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX. In some embodiments, the expression of one or more marker genes is decreased at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to untreated cells. In some embodiments, the expression of one or more marker genes, as a

group or a composite, is decreased at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% compared to untreated cells.

[0290] In some embodiments, described herein is a method of treating muscle atrophy in a subject, which comprises providing an siRNA antibody conjugate described herein and administering to the subject a therapeutically effective amount of the siRNA antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject. In some instances, the muscle atrophy is associated with FSHD. The siRNA antibody conjugate mediates RNA interference against the human DUX4 mRNA as to treat muscle atrophy in the subject, which comprises administering to the subject a therapeutically effective amount of the siRNA antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject.

[0291] In some embodiments, described herein is a method of treating muscle atrophy in a subject, which comprises providing a DUX4 siRNA antibody conjugate (DUX4 siRNA-conjugate or DUX4-AOC) described herein and administering to the subject a therapeutically effective amount of the DUX4 siRNA antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject. In some instances, the muscle atrophy is associated with FSHD. The DUX4 siRNA antibody conjugate mediates RNA interference against the human DUX4 mRNA as to treat muscle atrophy in the subject, which comprises administering to the subject a therapeutically effective amount of the DUX4 siRNA antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject.

[0292] In some embodiments, described herein is a method of treating FSHD in a subject, which comprises providing a DUX4 siRNA antibody conjugate (DUX4 siRNA conjugate or DUX4-AOC) described herein and administering to the subject a therapeutically effective amount of the DUX4 siRNA antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject. In some instances, the FSHD is FSHD type 1 (FSHD1). In some instances, the FSHD is FSHD type 2. The DUX4 siRNA antibody conjugate mediates RNA interference against the human DUX4 mRNA as to treat FSHD in the subject, which comprises administering to the subject a therapeutically effective amount of the DUX4 siRNA-conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject. In some embodiments, expression levels of one or more marker genes that are affected by DUX4 expression are also altered or modulated by the decreased expression levels of human DUX4. The DUX4 biomarker genes include but are not limited to MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX.

[0293] In some embodiments, described herein is a method of alleviating symptoms in a subject with FSHD, which comprises providing a DUX4 siRNA antibody conjugate (DUX4-siRNA conjugate or DUX4-AOC) described herein and administering to the subject a therapeutically effective amount of the siRNA conjugate described herein by reducing the levels of mRNA transcript of human DUX4. In some instances, the FSHD is FSHD type 1 (FSHD1). In some instances, the FSHD is FSHD type 2. In another embodiment, described herein is a method of alleviating symptoms in a FSHD patient, which comprises providing an

siRNA conjugate described herein and administering to the FSHD patient a therapeutically effective amount of the siRNA conjugate describes herein by reducing the levels of mRNA transcript of human DUX4 or reducing the levels of DUX4 protein.

[0294] In some instances, the symptoms of FSHD affect skeletal muscles. The skeletal muscles affected by FSHD include muscles around the eyes and mouth, muscle of the shoulders, muscle of the upper arms, muscle of the lower legs, abdominal muscles and hip muscles. In some instances, the symptoms of FSHD also affects vision and hearing. In some instances, the symptoms of FSHD also affect the function of the heart or lungs. In some instances, the symptoms of FSHD include muscle weakness, muscle atrophy, muscle dystrophy, pain inflammation, contractures, scoliosis, lordosis, hypoventilation, abnormalities of the retina, exposure to keratitis, mild hearing loss, and EMG abnormality.

[0295] In some embodiments, described herein is a method of improving skeletal muscle functions in a FSHD patient comprising the step of administering to the FSHD patient a therapeutically effective amount of the siRNA conjugate described herein by reducing the levels of mRNA transcript of human DUX4 or reducing the levels of DUX4 protein. In some instances, FSHD is FSHD type 1 (FSHD1). In some instances, FSHD is FSHD type 2. In some embodiments, described herein is a method of improving skeletal muscle functions, vision, hearing, heart functions or lung functions in a patient suffering from FSHD comprising the step of administering to the FSHD patient a therapeutically effective amount of the siRNA conjugate described herein by reducing the levels of mRNA transcript of human DUX4 or reducing the levels of DUX4 protein.

[0296] In some embodiments, described herein is a method of treating FSHD in a subject, which comprises providing an antisense oligonucleotide (ASO) antibody conjugate (ASO conjugate) described herein and administering to the subject a therapeutically effective amount of the ASO-antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject. In some instances, FSHD is FSHD type 1 (FSHD1). In some instances, FSHD is FSHD type 2. The ASO-conjugate mediates RNA interference against the human DUX4 mRNA as to treat FSHD in the subject, which comprises administering to the subject a therapeutically effective amount of the ASO-antibody conjugate described herein and reducing the levels of mRNA transcript of human DUX4 in said subject. In some embodiments, expression levels of one or more marker genes that are affected by DUX4 expression is also altered or modulated by the decreased expression levels of human DUX4. The DUX4 biomarker genes include but are not limited to MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX.

[0297] In some embodiments, described herein is a method of treating FSHD in a subject. In some instances, the FSHD subject suffers from FSHD1. In other instances, the FSHD subject suffers from FSHD2. In another embodiment, the FSHD subject has muscle cells abnormally expressing DUX4 protein caused by the genetic and epigenetic molecular changes in the D4Z4 region of the long arm of chromosome 4. The genetic molecular changes in the muscle cells are mutations leading to the contraction of the D4Z4 region containing 1-10 repeats instead of the normal 11 to 100 repeats of chromosome 4 of the FSHD subject. The epigen-

etic molecular changes in the muscle cells are changes leading to the hypomethylation of the D4Z4 region of chromosome 4 of the FSHD subject. In some instances, the muscle cells are skeletal muscle cells.

Pharmaceutical Formulation

[0298] In some embodiments, the pharmaceutical formulations described herein are administered to a subject by multiple administration routes, including but not limited to, parenteral (e.g., intravenous, subcutaneous, intramuscular), oral, intranasal, buccal, rectal, or transdermal administration routes. In some instances, the pharmaceutical composition describe herein is formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intra-arterial, intraperitoneal, intrathecal, intracerebral, intracerebroventricular, or intracranial) administration. In other instances, the pharmaceutical composition describe herein is formulated for oral administration. In still other instances, the pharmaceutical composition describe herein is formulated for intranasal administration.

[0299] In some embodiments, the pharmaceutical formulations include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations (e.g., nanoparticle formulations), and mixed immediate and controlled release formulations.

[0300] In some instances, the pharmaceutical formulation includes multiparticulate formulations. In some instances, the pharmaceutical formulation includes nanoparticle formulations. In some instances, nanoparticles comprise cMAP, cyclodextrin, or lipids. In some cases, nanoparticles comprise solid lipid nanoparticles, polymeric nanoparticles, self-emulsifying nanoparticles, liposomes, microemulsions, or micellar solutions. Additional exemplary nanoparticles include, but are not limited to, paramagnetic nanoparticles, superparamagnetic nanoparticles, metal nanoparticles, fullerene-like materials, inorganic nanotubes, dendrimers (such as with covalently attached metal chelates), nanofibers, nanohorns, nano-onions, nanorods, nanoropes and quantum dots. In some instances, a nanoparticle is a metal nanoparticle, e.g., a nanoparticle of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, niobium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, hafnium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, gadolinium, aluminum, gallium, indium, tin, thallium, lead, bismuth, magnesium, calcium, strontium, barium, lithium, sodium, potassium, boron, silicon, phosphorus, germanium, arsenic, antimony, and combinations, alloys or oxides thereof.

[0301] In some instances, a nanoparticle includes a core or a core and a shell, as in a core-shell nanoparticle.

[0302] In some instances, a nanoparticle is further coated with molecules for attachment of functional elements (e.g., with one or more of a polynucleic acid molecule or binding moiety described herein). In some instances, a coating comprises chondroitin sulfate, dextran sulfate, carboxymethyl dextran, alginic acid, pectin, carrageenan, fucoidan, agarose, porphyran, karaya gum, gellan gum, xanthan gum, hyaluronic acids, glucosamine, galactosamine, chitin

(or chitosan), polyglutamic acid, polyaspartic acid, lysozyme, cytochrome C, ribonuclease, trypsinogen, chymotrypsinogen, α -chymotrypsin, polylysine, polyarginine, histone, protamine, ovalbumin or dextrin or cyclodextrin. In some instances, a nanoparticle comprises a graphene-coated nanoparticle.

[0303] In some cases, a nanoparticle has at least one dimension of less than about 500 nm, 400 nm, 300 nm, 200 nm, or 100 nm.

[0304] In some instances, the nanoparticle formulation comprises paramagnetic nanoparticles, superparamagnetic nanoparticles, metal nanoparticles, fullerene-like materials, inorganic nanotubes, dendrimers (such as with covalently attached metal chelates), nanofibers, nanohorns, nano-onions, nanorods, nanoropes or quantum dots. In some instances, a polynucleic acid molecule or a binding moiety described herein is conjugated either directly or indirectly to the nanoparticle. In some instances, at least 1, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more polynucleic acid molecules or binding moieties described herein are conjugated either directly or indirectly to a nanoparticle.

[0305] In some embodiments, the pharmaceutical formulation comprises a delivery vector, e.g., a recombinant vector, the delivery of the polynucleic acid molecule into cells. In some instances, the recombinant vector is DNA plasmid. In other instances, the recombinant vector is a viral vector. Exemplary viral vectors include vectors derived from adeno-associated virus, retrovirus, adenovirus, or alphavirus. In some instances, the recombinant vectors capable of expressing the polynucleic acid molecules provide stable expression in target cells. In additional instances, viral vectors are used that provide for transient expression of polynucleic acid molecules.

[0306] In some embodiments, the pharmaceutical formulation includes a carrier or carrier materials selected on the basis of compatibility with the composition disclosed herein, and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. Pharmaceutically compatible carrier materials include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, polyvinylpyrrolidone (PVP), cholesterol, cholesterol esters, sodium caseinate, soy lecithin, taurocholic acid, phosphotidylcholine, sodium chloride, tricalcium phosphate, dipotassium phosphate, cellulose and cellulose conjugates, sugars sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H. A, and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[0307] In some instances, the pharmaceutical formulation further includes pH adjusting agents or buffering agents which include acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymeth-

ylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[0308] In some instances, the pharmaceutical formulation includes one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[0309] In some instances, the pharmaceutical formulation further includes diluent which are used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In certain instances, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel®; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac® (Amstar); mannitol, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

[0310] In some cases, the pharmaceutical formulation includes disintegration agents or disintegrants to facilitate the breakup or disintegration of a substance. The term "disintegrate" include both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid. Examples of disintegration agents include a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia® and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[0311] In some instances, the pharmaceutical formulation includes filling agents such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sul-

fate, microcrystalline cellulose, cellulose powder, dextrose, dextrans, dextrans, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[0312] Lubricants and glidants are also optionally included in the pharmaceutical formulations described herein for preventing, reducing or inhibiting adhesion or friction of materials. Exemplary lubricants include, e.g., stearic acid, calcium hydroxide, talc, sodium stearyl fumarate, a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil (Sterotex®), higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol (e.g., PEG-4000) or a methoxypolyethylene glycol such as Carbowax®, sodium oleate, sodium benzoate, glyceryl behenate, polyethylene glycol, magnesium or sodium lauryl sulfate, colloidal silica such as Syloid™, Cab-O-Sil®, a starch such as corn starch, silicone oil, a surfactant, and the like.

[0313] Plasticizers include compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. Plasticizers also function as dispersing agents or wetting agents.

[0314] Solubilizers include compounds such as triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium docusate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200-600, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide and the like.

[0315] Stabilizers include compounds such as any anti-oxidation agents, buffers, acids, preservatives and the like.

[0316] Suspending agents include compounds such as polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, vinyl pyrrolidone/vinyl acetate copolymer (S630), polyethylene glycol, e.g., the polyethylene glycol has a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose acetate stearate, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, celluloses, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[0317] Surfactants include compounds such as sodium lauryl sulfate, sodium docusate, Tween 60 or 80, triacetin, vitamin E TPGS, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g. Pluronic® (BASF), and the like. Additional surfactants include polyoxyethylene fatty acid

glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40. Sometimes, surfactants is included to enhance physical stability or for other purposes.

[0318] Viscosity enhancing agents include, e.g., methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetate stearate, hydroxypropylmethyl cellulose phthalate, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

[0319] Wetting agents include compounds such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium docusate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, Tween 80, vitamin E TPGS, ammonium salts and the like.

Therapeutic Regimens

[0320] In some embodiments, the pharmaceutical compositions described herein are administered for therapeutic applications. In some embodiments, the pharmaceutical composition is administered once per day, twice per day, three times per day or more. The pharmaceutical composition is administered daily, every day, every alternate day, five days a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month, three times per month, once in two months, once in three months, once in four months, once in five months, once in six months or more. The pharmaceutical composition is administered for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 18 months, 2 years, 3 years, or more.

[0321] In some embodiments, one or more pharmaceutical compositions are administered simultaneously, sequentially, or at an interval period of time. In some embodiments, one or more pharmaceutical compositions are administered simultaneously. In some cases, one or more pharmaceutical compositions are administered sequentially. In additional cases, one or more pharmaceutical compositions are administered at an interval period of time (e.g., the first administration of a first pharmaceutical composition is on day one followed by an interval of at least 1, 2, 3, 4, 5, or more days prior to the administration of at least a second pharmaceutical composition).

[0322] In some embodiments, two or more different pharmaceutical compositions are co-administered. In some instances, the two or more different pharmaceutical compositions are co-administered simultaneously. In some cases, the two or more different pharmaceutical compositions are co-administered sequentially without a gap of time between administrations. In other cases, the two or more different pharmaceutical compositions are co-administered sequentially with a gap of about 0.5 hour, 1 hour, 2 hour, 3 hour, 12 hours, 1 day, 2 days, or more between administrations.

[0323] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the composition is given continuously; alternatively, the dose of the composition being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In some instances, the length of the drug holiday varies between 2 days and 1 year, including

by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday is from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[0324] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained.

[0325] In some embodiments, the amount of a given agent that correspond to such an amount varies depending upon factors such as the particular compound, the severity of the disease, the identity (e.g., weight) of the subject or host in need of treatment, but nevertheless is routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, and the subject or host being treated. In some instances, the desired dose is conveniently presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0326] The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages is altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[0327] In some embodiments, toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD50 and ED50. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with minimal toxicity. The dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

Kits/Article of Manufacture

[0328] Disclosed herein, in certain embodiments, are kits and articles of manufacture for use with one or more of the compositions and methods described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials,

syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[0329] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[0330] For example, the container(s) include target nucleic acid molecule described herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[0331] A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[0332] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[0333] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Certain Terminology

[0334] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[0335] As used herein, ranges and amounts can be expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 μL ” means “about 5 μL ” and also “5 μL .” Generally, the term “about” includes an amount that would be expected to be within experimental error.

[0336] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0337] As used herein, the terms “individual(s)”, “subject (s)” and “patient(s)” mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician’s assistant, an orderly or a hospice worker).

[0338] The term “therapeutically effective amount” relates to an amount of a polynucleic acid molecule conjugate that is sufficient to provide a desired therapeutic effect in a mammalian subject. In some cases, the amount is single or multiple dose administration to a patient (such as a human) for treating, preventing, preventing the onset of, curing, delaying, reducing the severity of, ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the patient beyond that expected in the absence of such treatment. Naturally, dosage levels of the particular polynucleic acid molecule conjugate employed to provide a therapeutically effective amount vary in dependence of the type of injury, the age, the weight, the gender, the medical condition of the subject, the severity of the condition, the route of administration, and the particular inhibitor employed. In some instances, therapeutically effective amounts of polynucleic acid molecule conjugate, as described herein, is estimated initially from cell culture and animal models. For example, IC_{50} values determined in cell culture methods optionally serve as a starting point in animal models, while ICs values determined in animal models are optionally used to find a therapeutically effective dose in humans.

[0339] Skeletal muscle, or voluntary muscle, is generally anchored by tendons to bone and is generally used to effect skeletal movement such as locomotion or in maintaining posture. Although some control of skeletal muscle is generally maintained as an unconscious reflex (e.g., postural muscles or the diaphragm), skeletal muscles react to conscious control. Smooth muscle, or involuntary muscle, is found within the walls of organs and structures such as the esophagus, stomach, intestines, uterus, urethra, and blood vessels.

[0340] Skeletal muscle is further divided into two broad types: Type I (or “slow twitch”) and Type II (or “fast twitch”). Type I muscle fibers are dense with capillaries and are rich in mitochondria and myoglobin, which gives Type I muscle tissue a characteristic red color. In some cases, Type I muscle fibers carries more oxygen and sustain aerobic activity using fats or carbohydrates for fuel. Type I muscle fibers contract for long periods of time but with little force. Type II muscle fibers are further subdivided into three major subtypes (IIa, IIx, and IIb) that vary in both contractile speed and force generated. Type II muscle fibers contract quickly and powerfully but fatigue very rapidly, and therefore produce only short, anaerobic bursts of activity before muscle contraction becomes painful.

[0341] Unlike skeletal muscle, smooth muscle is not under conscious control.

[0342] Cardiac muscle is also an involuntary muscle but more closely resembles skeletal muscle in structure and is found only in the heart. Cardiac and skeletal muscles are striated in that they contain sarcomeres that are packed into highly regular arrangements of bundles. By contrast, the myofibrils of smooth muscle cells are not arranged in sarcomeres and therefore are not striated.

[0343] Muscle cells encompass any cells that contribute to muscle tissue. Exemplary muscle cells include myoblasts, satellite cells, myotubes, and myofibril tissues.

[0344] As used here, muscle force is proportional to the cross-sectional area (CSA), and muscle velocity is proportional to muscle fiber length. Thus, comparing the cross-sectional areas and muscle fibers between various kinds of muscles is capable of providing an indication of muscle atrophy. Various methods are known in the art to measure muscle strength and muscle weight, see, for example, “Musculoskeletal assessment; Joint range of motion and manual muscle strength” by Hazel M. Clarkson, published by Lippincott Williams & Wilkins, 200). The production of tomographic images from selected muscle tissues by computed axial tomography and sonographic evaluation are additional methods of measuring muscle mass.

[0345] The term antibody oligonucleotide conjugate (AOC) refers to an antibody conjugated to a nucleotide.

[0346] The term siRNA conjugate or siRNA antibody conjugate refers to an antibody conjugated to a siRNA.

[0347] The term DUX4 siRNA-conjugate or DUX4 siRNA antibody conjugate refers to an antibody conjugated to a siRNA hybridizing to a target sequence of the human DUX4 mRNA.

[0348] The term DUX4-AOC refers to an antibody conjugated to an siRNA hybridizing to a target sequence of the human DUX4 mRNA.

EXAMPLES

[0349] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1. Bioinformatic siRNA Library Design Against Human Full Length DUX4 Transcript

[0350] FIG. 2 shows a flowchart of in silico selection process of DUX4 siRNA. Sequences of all siRNAs that can bind to DUX4, or a pre-determined region of the DUX4 are collected to generate a starting set of DUX4 siRNA. From the starting set of DUX siRNAs, the first eliminating step comprises eliminating one or more DUX siRNAs that has single nucleotide polymorphism (SNP) and/or MEF<-5. Then, the second eliminating step comprises eliminating DUX siRNAs with 0 and 1 MM in the human transcriptome (such that only hits allowed are DUX, DUX5, and DBET). Then, the third eliminating step comprises eliminating DUX siRNAs with 0 mismatch (MM) in the human intragenic regions (such that only hits allowed are DUX1, DUX5 and DBET pseudogenes). Then, the next eliminating step comprises eliminating DUX siRNAs with a MM to DUX4 human sequence used in FLExDUX4 FSHD mouse model. Then, the next step is carrying forward only or one or more DUX siRNAs with predicted viability >60. Next, the eliminating step comprises eliminating one or more DUX siRNAs

with a match to a seed region of known miRNAs 1-1000. Then, the eliminating step continues with eliminating DUX siRNAs molecule with % GC content 75 and above. Then, the final selection process comprises with 8 or less predicted off-target hits with 2 MM, except for the region 295-1132, for which up to 12 hits are allowed. Using such series of selection steps, final 70 candidate DUX siRNAs could be selected from a starting set of 1694 DUX siRNAs. FIG. 3 shows the location and numbers of such selected DUX4 siRNA in the DUX4 mRNA transcript (NM_001306068).

[0351] Identified siRNA candidates share common characteristics in their sequences as shown below Table 10 The identified siRNAs have mostly 2'-O-Me modifications, with

2'-F modifications only located on sense strand at positions 7, 8, 9 and 2'-F only located on antisense strand at positions 1, 2, 6, 14, 16. Also, the identified siRNAs comprises 4 thioate modifications on each strand, located at the final 2 linkages of each 5' and 3' terminus. The identified siRNAs further comprises "UP" at the first position of 5' end of the antisense strand, regardless of the actual target mRNA sequence (coupled with "a" at the last position at the 3' end of the sense strand). The identified siRNAs further comprises "uu" overhang at the 3' end of the antisense strand only, with no overhang at the 3' end of the sense strand. The optimization of the identified siRNAs may comprise a vinyl phosphonate nucleotide, an inverted abasic moiety, or an amine linker to the passenger strand or the guide strand.

TABLE 10

duplex name	sense strand sequence (5'-3') (passenger strand)	antisense strand sequence (5'-3') (guide strand)
DUX4 template	nsnsnnnnNfNfNfnnnnnnsnsa	UfsNfsnnnNfnnnnnnNfnNfnnsusu

vpN = vinyl phosphonate 2'-MOE;
 upper case (N) = 2'-OH (ribo);
 lower case (n) = 2'-O-Me (methyl) dN = 2'-H (deoxy);
 Nf = 2'-F (fluoro);
 s = phosphorothioate backbone modification;
 iB = inverted abasic

[0352] Tables 11, 12, and 13 illustrate identified siRNA candidates for the regulation of human DUX4.

TABLE 11

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_11_29	11	1	cgacaccctcggacagcac	71	gtgctgtccgagggtgtcg
NM_001306068_57_75	57	2	acggcgacggagactcggt	72	aacgagtctccgtcgccgt
NM_001306068_58_76	58	3	cggcgacggagactcgttt	73	aaacgagtctccgtcgccg
NM_001306068_59_77	59	4	ggcgacggagactcgtttg	74	caaacgagtctccgtcgcc
NM_001306068_60_78	60	5	gcgacggagactcgtttgg	75	ccaaacgagtctccgtcgc
NM_001306068_61_79	61	6	cgacggagactcgtttggga	76	tccaaacgagtctccgtcg
NM_001306068_62_80	62	7	gacggagactcgtttggac	77	gtccaaacgagtctccgtc
NM_001306068_63_81	63	8	acggagactcgtttggacc	78	ggtccaaacgagtctccgt
NM_001306068_77_95	77	9	ggaccccgagccaaagcga	79	tcgctttggctcggggctc
NM_001306068_78_96	78	10	gaccccgagccaaagcgag	80	ctcgctttggctcggggctc
NM_001306068_79_97	79	11	accccgagccaaagcgagg	81	cctcgctttggctcgggggt
NM_001306068_99_117	99	12	cctcgagcctgctttgag	82	ctcaaagcaggctcgagg
NM_001306068_102_120	102	13	gcgagcctgctttgagcgg	83	ccgctcaaagcaggctcgc
NM_001306068_137_155	137	14	tcgccaccagagaacggct	84	agccgttctctggtggcga
NM_001306068_160_178	160	15	caggccatcggcattccgg	85	ccggaatgccgatggcctg
NM_001306068_162_180	162	16	ggccatcggcattccggag	86	ctccggaatgccgatggcc
NM_001306068_163_181	163	17	gccatcggcattccggagc	87	gctccggaatgccgatggc
NM_001306068_231_249	231	18	gcaccggcgggaatctcgg	88	ccgagattcccgcgggtgc

TABLE 11-continued

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_232_250	232	19	caccggcgggaatctcggc	89	gccgagattcccggcggtg
NM_001306068_274_292	274	20	ccagaaggccggcgaaagc	90	gctttcgccggccttctgg
NM_001306068_276_294	276	21	agaaggccggcgaaagcgg	91	ccgctttcgccggccttct
NM_001306068_277_295	277	22	gaaggccggcgaaagcggga	92	tccgctttcgccggccttc
NM_001306068_285_303	285	23	gcgaaagcggaccgccgtc	93	gacggcgggtccgctttcgc
NM_001306068_287_305	287	24	gaaagcggaccgccgtcac	94	gtgacggcgggtccgcttcc
NM_001306068_292_310	292	25	cgaccgccgtcaccggat	95	atccggtgacggcgggtccg
NM_001306068_293_311	293	26	ggaccgccgtcaccggatc	96	gatccggtgacggcgggtcc
NM_001306068_294_312	294	27	gaccgccgtcaccggatcc	97	ggatccggtgacggcgggtc
NM_001306068_389_407	389	28	agacgggcctcccggagtc	98	gactccgggagggcccgtct
NM_001306068_524_542	524	29	cctcgtgggtcgccttcgc	99	gcgaaggcgaccacagagg
NM_001306068_525_543	525	30	ctcgtgggtcgccttcgcc	100	ggcgaaggcgaccacagag
NM_001306068_679_697	679	31	gaggggatctcccaacctg	101	caggttgggagatcccctc
NM_001306068_704_722	704	32	cgcgcggggatttcgccta	102	taggcgaaatcccgcgcg
NM_001306068_705_723	705	33	gcgcggggatttcgcctac	103	gtaggcgaaatcccgcgc
NM_001306068_708_726	708	34	cggggatttcgcctacgcc	104	ggcgtaggcgaaatccccg
NM_001306068_893_911	893	35	tgcttgcccaccacagtc	105	gacgtgggtggcgcaagca
NM_001306068_1132_1150	1132	36	ctggcgagccggagtttc	106	gaaactccgggctcgccag
NM_001306068_1134_1152	1134	37	ggcgagccggagtttctg	107	cagaaactccgggctcgcc
NM_001306068_1158_1176	1158	38	ggcgcaacctctcctagaa	108	ttctaggagaggttgcgcc
NM_001306068_1159_1177	1159	39	gcgcaacctctcctagaaa	109	tttctaggagaggttgcg
NM_001306068_1163_1181	1163	40	aacctctcctagaacgga	110	tccgttctaggagaggtt
NM_001306068_1236_1254	1236	41	cagcgaggaagaataccgg	111	ccggtattcttctcgcctg
NM_001306068_1237_1255	1237	42	agcgaggaagaataccggg	112	cccggattcttctcgcct
NM_001306068_1238_1256	1238	43	gcgaggaagaataccgggc	113	gcccgtattcttctcctcgc
NM_001306068_1284_1302	1284	44	gttgggacgggtcgggtg	114	caccgcaccccgctccaac
NM_001306068_1290_1308	1290	45	acggggtcgggtggttcgg	115	ccgaaccaccgcaccccg
NM_001306068_1294_1312	1294	46	ggtcgggtggttcggggca	116	tgccccgaaccaccgcacc
NM_001306068_1295_1313	1295	47	gtcgggtggttcggggcag	117	ctgccccgaaccaccgcac
NM_001306068_1315_1333	1315	48	gcggtggcctctctttcgc	118	gcgaaagagaggccaccgc
NM_001306068_1316_1334	1316	49	cggtggcctctctttcgcg	119	cgcgaaagagaggccaccg
NM_001306068_1317_1335	1317	50	ggtggcctctctttcgcgg	120	ccgcgaaagagaggccacc
NM_001306068_1321_1339	1321	51	gcctctctttcgcggggaa	121	ttccccgcgaaagagaggc
NM_001306068_1340_1358	1340	52	cacctggtggtcaccggag	122	ctccgtagccagccagggtg
NM_001306068_1350_1368	1350	53	gctaccgaggggctgtct	123	agacacgcccctccgtagc
NM_001306068_1351_1369	1351	54	ctaccgaggggctgtctc	124	gagacacgcccctccgtag
NM_001306068_1539_1557	1539	55	acgtgcaaggagctcgc	125	agcgagctcccttgcacgt

TABLE 11-continued

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_1540_1558	1540	56	cgtgcaagggagctcgctg	126	cagcgagctcccttgcaacg
NM_001306068_1541_1559	1541	57	gtgcaagggagctcgctgg	127	ccagcgagctcccttgcaac
NM_001306068_1610_1628	1610	58	caccttcgacgctgtctta	128	tagacagcgtcggaaggtg
NM_001306068_1611_1629	1611	59	accttcgacgctgtctag	129	ctagacagcgtcggaaggt
NM_001306068_1612_1630	1612	60	ccttcgacgctgtctagg	130	cctagacagcgtcggaag
NM_001306068_1613_1631	1613	61	cttcgacgctgtctaggc	131	gcctagacagcgtcggaag
NM_001306068_1615_1633	1615	62	tccgacgctgtctaggcaa	132	ttgcctagacagcgtcgga
NM_001306068_1616_1634	1616	63	ccgacgctgtctaggcaaa	133	ttgcctagacagcgtcgga
NM_001306068_1619_1637	1619	64	acgctgtctaggcaaacct	134	aggtttgcctagacagcgt
NM_001306068_1632_1650	1632	65	aaacctggattagagttac	135	gtaactctaataccaggttt
NM_001306068_336_354	336	66	ctttgagaaggatcgcttt	136	aaagcgatccttctcaaac
NM_001306068_672_690	672	67	gccggcagaggggatctcc	137	ggagatcccctctgccggc
NM_001306068_882_900	882	68	gggccaaggggtgcttgccg	138	cgcaagcacccttgcccc
NM_001306068_884_902	884	69	gccaaaggggtgcttgccgc	139	ggcgcaagcacccttgccc
NM_001306068_1045_1063	1045	70	atgcaaggcatcccggcgc	140	gcgccgggatgccttgcac

TABLE 12

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_11_29	11	141	csgsacacCfCfUfcggac	211	UfsUfsgcuGfuccgaggGfuGfucgsusu
NM_001306068_57_75	57	142	ascsggcgAfCfGfgagac	212	UfsAfscgaGfucuccguCfGfcgususu
NM_001306068_58_76	58	143	csgsgcgaCfGfGfagacu	213	UfsAfsacgAfgucuccGfGfcgcsusu
NM_001306068_59_77	59	144	gsgscgacGfGfAfgacuc	214	UfsAfsaacGfagucuccGfuCfGCCSusu
NM_001306068_60_78	60	145	gscsgacgGfAfgfacucg	215	UfsCfsaaaCfagucucCfGfGfcgsusu
NM_001306068_61_79	61	146	csgsacggAfGfAfcucgu	216	UfsCfscaaAfcgagucucfcGfucgsusu
NM_001306068_62_80	62	147	gsasccggaGfAfcfucguu	217	UfsUfsccaAfacgagucUfcCfGucgsusu
NM_001306068_63_81	63	148	ascsggagAfCfUfcguuu	218	UfsGfsuccAfaacgaguCfucfcgususu
NM_001306068_77_95	77	149	gsgsacccCfGfAfgccaa	219	UfsCfsgcuUfuggcucGfGfuccsusu
NM_001306068_78_96	78	150	gsasccccGfAfgfcaaaa	220	UfsUfscgcUfuuggcucGfGfGucgsusu
NM_001306068_79_97	79	151	ascsccegAfGfCfcaaac	221	UfsCfsucgCfuuggcucCfGfGgususu

TABLE 12-continued

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_99_117	99	152	cscsugcgAfGfCfcugcu uugsasa	222	UfsUfscaaAfgcaggcu CfGcfaggssusu
NM_001306068_102_120	102	153	gscsgagcCfUfGfcuuug agcsgsa	223	UfsCfsgcuCfaaagcagG fcUfcgcsusu
NM_001306068_137_155	137	154	uscsgccaCfCfAfgagaa cggscsa	224	UfsGfscggUfucucugg UfgGfcgasusu
NM_001306068_160_178	160	155	csasggccAfUfCfggcau uccsgsa	225	UfsCfsggaAfugccgau GfGcfucgsusu
NM_001306068_162_180	162	156	gsgsccauCfGfGfcuuuc cgggsasa	226	UfsUfscggGfaaugccg AfuGfGCCsusu
NM_001306068_163_181	163	157	gscscacuGfGfCfauucc ggasgsa	227	UfsCfSuccGfgaaugcc GfaUfggcsusu
NM_001306068_231_249	231	158	gscsaccgGfCfGfGgaau cucsgsa	228	UfsCfSgagAfuucccgC CfGfGfugcsusu
NM_001306068_232_250	232	159	csascggCfGfGfGaauc ucgsgsa	229	UfsCfscgaGfaucccgC fcGfGfugcsusu
NM_001306068_274_292	274	160	cscsagaaGfGfCfcggcg aaaagsa	230	UfsCfSuuuCfGCCggcc UfuCfuggssusu
NM_001306068_276_294	276	161	asgsaaggCfCfGfGcga agcsgsa	231	UfsCfsgcuUfucgccc CfcUfucususu
NM_001306068_277_295	277	162	gsasaggcCfGfGfcgaaa gcgsgsa	232	UfsCfscgcUfuucgccc GfcCfuucsusu
NM_001306068_285_303	285	163	gscsgaaaGfCfGfGaccg ccgsusa	233	UfsAfscggCfGgucggc UfuUfcgcsusu
NM_001306068_287_305	287	164	gsasaagcGfGfAfccgcc gucsasa	234	UfsUfsgacGfGcggucc GfcUfuucsusu
NM_001306068_292_310	292	165	csgsgaccGfCfCfGfucac cgggsasa	235	UfsUfscggGfugacggc GfGfUfcgcsusu
NM_001306068_293_311	293	166	gsgsaccgCfCfGfucacc ggasusa	236	UfsAfSuccGfGugacgg CfGfGfuccsusu
NM_001306068_294_312	294	167	gsasccgcCfGfUfcaccg gauscasa	237	UfsGfSaucCfGgugacg GfcGfGfucsusu
NM_001306068_389_407	389	168	asgsaccgGfCfCfucaccg gagsusa	238	UfsAfscucCfGggaggc CfcGfucususu
NM_001306068_524_542	524	169	cscsucguGfGfGfucgcc uucsgsa	239	UfsCfsgaaGfGcgaccA fcGfaggssusu
NM_001306068_525_543	525	170	csuscgugGfGfUfcgccu ucgscsa	240	UfsGfscgaAfggcgacc CfaCfGfagsusu
NM_001306068_679_697	679	171	gsasggggAfUfCfuccca accsusa	241	UfsAfsgguUfgggagau CfcCfcucsusu
NM_001306068_704_722	704	172	csgscgGfGfGfauuuc gccsusa	242	UfsAfsggcGfaaaucC fgCfGcgsusu
NM_001306068_705_723	705	173	gscsgcggGfGfAfuuuc gccusasa	243	UfsUfsaggCfGaaauccC fcGfGcgsusu
NM_001306068_708_726	708	174	csgsgggaUfUfUfcgccu acgscsa	244	UfsGfscguAfggCGaaa UfcCfcgcsusu
NM_001306068_893_911	893	175	usgscuugCfGfCfCacc acgsusa	245	UfsAfscguGfGggggcg CfaAfgcasusu

TABLE 12-continued

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_1132_1150	1132	176	csusggcgAfGfCfccgga guususa	246	UfsAfsaacUfccgggcu CfgCfcagsusu
NM_001306068_1134_1152	1134	177	gsgscgagCfCfCfaggagu uucsusa	247	UfsAfsгааAfcuccggg CfuCfгccsusu
NM_001306068_1158_1176	1158	178	gsgscgcaAfCfCfucucc uagsasa	248	UfsUfsсuaGfgagaggu UfgCfгccsusu
NM_001306068_1159_1177	1159	179	gscsgcaaCfCfUfcuccu agasasa	249	UfsUfsucuAfggagagg UfuGfгсsusu
NM_001306068_1163_1181	1163	180	asascucUfCfCfuagaa acgsgsa	250	UfsCfссguUfucuagga GfaGfгuususu
NM_001306068_1236_1254	1236	181	csasgcgaGfGfAfgaaу accsgsa	251	UfsCfсгguAfuucuucc UfcGfгсгsusu
NM_001306068_1237_1255	1237	182	asgscgagGfAfgaaуаа ccgsgsa	252	UfsCfсггUfaucuuc CfuCfгссsusu
NM_001306068_1238_1256	1238	183	gscsgaggAfAfgaaуac cggsgsa	253	UfsCfссгGfuauucu CfcUfгссsusu
NM_001306068_1284_1302	1284	184	gsusugggAfCfGfггgu cgggsusa	254	UfsAfscccGfaccссguC fcCfaacsusu
NM_001306068_1290_1308	1290	185	ascsggggUfCfGfггггг guucsgsa	255	UfsCfсгааCfcaccссgaC fcCfгсгsusu
NM_001306068_1294_1312	1294	186	gsgsucggGfUfGfггггг ggggsasa	256	UfsGfсcccCfгаaccacC fcGfaccsusu
NM_001306068_1295_1313	1295	187	gsuscgggUfGfGfuucg gggсsasa	257	UfsUfsгссCfcгаaccacC fcCfгссsusu
NM_001306068_1315_1333	1315	188	gscsggггGfCfCfucucu uucsgsa	258	UfsCfсгааAfgagagg CfaCfгссsusu
NM_001306068_1316_1334	1316	189	csгsgгггCfCfUfcucu ucгссsa	259	UfsGfссгаAfgagagg CfcAfcгссsusu
NM_001306068_1317_1335	1317	190	gsgsuggcCfUfCfucuuу ccгсгsa	260	UfsCfсггсAfaagagag GfcCfaccsusu
NM_001306068_1321_1339	1321	191	gscscucuCfUfUfucггг gggсasa	261	UfsUfscccCfгсгааagA fgAfgгсsusu
NM_001306068_1340_1358	1340	192	csascugGfCfUfггссua cggсasa	262	UfsUfsccгUfagccagcC faGfггсsusu
NM_001306068_1350_1368	1350	193	gscsuacgGfAfgfггггггг ugucsa	263	UfsGfсsacaCfгсcccucC fgUfagсsusu
NM_001306068_1351_1369	1351	194	csusacggAfGfGfггггггг gucsusa	264	UfsAfsггacAfcгсcccucC fcGfuagsusu
NM_001306068_1539_1557	1539	195	ascsgugcAfAfgfггггггг ucгссsa	265	UfsGfссгаGfcucccuу GfcAfcгссsusu
NM_001306068_1540_1558	1540	196	csгsugcaAfgfггггггггггг cгссusa	266	UfsAfsггггAfgcucccu UfgCfaccссsusu
NM_001306068_1541_1559	1541	197	gsusgcaaGfGfггггггггггг gcusgsa	267	UfsCfсггггGfagcucccU fuGfсссsusu
NM_001306068_1610_1628	1610	198	csascуuCfCfGfггггггггггг gucsusa	268	UfsAfsггггAfgггггггггггг AfaGfггсsusu
NM_001306068_1611_1629	1611	199	ascscuucCfGfAfcггггггг ucusasa	269	UfsUfsagaCfagггггггггггг GfaAfgгсsusu
NM_001306068_1612_1630	1612	200	cscsuuccGfAfcггггггггггг cuasgsa	270	UfsCfсsuagAfcггггггггггг GfgAfgгсsusu

TABLE 12-continued

Name	19mer start site	SEQ ID NO	sense/passenger_seq (5'-3')	SEQ ID NO	antisense/guide_seq (5'-3')
NM_001306068_1613_1631	1613	201	csusuccgAfCfGfcuguc uagsgsa	271	UfsCfscuaGfacagcguc fgGfaagsusu
NM_001306068_1615_1633	1615	202	uscscgacGfCfUfgucua ggcsasa	272	UfsUfsgccUfagacagc GfuCfggasusu
NM_001306068_1616_1634	1616	203	cscsgacGfUfGfucua gcasasa	273	UfsUfsugcCfuagacag CfUfcggsusu
NM_001306068_1619_1637	1619	204	ascsgcugUfCfUfaggca aacsasa	274	UfsGfsguuUfgccuaga CfAGfcgususu
NM_001306068_1632_1650	1632	205	asasaccuGfGfAfuuaa guusasa	275	UfsUfsaacUfcuaaaccA fgGfuususu
NM_001306068_336_354	336	206	csusuugaGfAfAfggauc gcususa	276	UfsAfsagcGfaucuuuc UfAfaagsusu
NM_001306068_672_690	672	207	gscscggcAfGfAfgggga ucusasa	277	UfsGfsagaUfccccuc GfCfggcsusu
NM_001306068_882_900	882	208	gsgsgccaAfGfGfggugc uugscsa	278	UfsGfscaaGfcacccuU fgGfcccusu
NM_001306068_884_902	884	209	gscscaagGfGfGfugcuu gcgscsa	279	UfsGfscgcAfagcaccC fuUfggcsusu
NM_001306068_1045_1063	1045	210	asusgcaaGfGfCfaucgc ggcsasa	280	UfsCfsgccGfggaucc UfUGfcaususu

vpN = vinyl phosphonate 21-MOE; upper case (N) = 2'-OH (ribo); lower case (n) = 2'-O-Me (methyl)
 dN = 2'-H (deoxy); NF = 2'-F (fluoro); s = phosphorothioate backbone modification; iB = inverted abasic

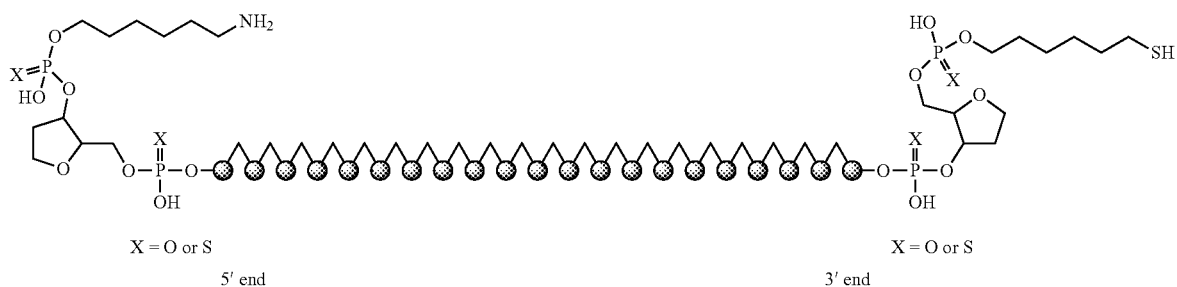
TABLE 13

SEQ ID NO	sense/passenger seq (5'-3')	SEQ ID NO	antisense/guide seq (5'-3')
371	CTGCCTCTCCACCAGCCCA	372	TGGGCTGGTGGAGAGGCAG
373	GCAGAGATGGAGAGAGGAA	374	TTCCTCTCTCCATCTCTGC
375	GCGGTTTCCTCCGGGACAA	376	TTGTCCCGGAGGAAACCGC
377	GGACGACGGAGGCGTGATT	378	AATCACGCCTCCGTCGTCC
379	CGGCACCCCGAAACATGCAGGGAA	380	TTCCTGCATGTTTCCGGTGCCCG
381	CCGGAACATGCAGGGAAG	382	CTTCCCTGCATGTTCCGG
383	GAAATGAACGAGAGCCACA	384	TGTGGCTCTCGTTCATTTT
385	TGGCACACTCAAGACTCCCACGGAG	386	CTCCGTGGGAGTCTTGAGTGTGCCA
387	CCACGGAGGTTAGTTCCA	388	TGGAAGTGAACCTCCGTGG
389	ACCACCACCACCACCACCA	390	TGGTGGTGGTGGTGGTGGT
391	CGCATTCATGAAGGGGTG	392	CACCCCTTCATGAATGGCG
393	CATGAAGGGGTGGAGCCTG	394	CAGGCTCCACCCCTTCATG
395	GAGCCTGCTTTGAGCGGAA	396	TTCCGCTCAAAGCAGGCTC
397	CCGAGCCTTTGAGAAGGATCGCTT	398	AAAGCGATCCTTCTCAAAGGCTCGG
399	GGCAGGCGCCCGCGCAGG	400	CCTGCGCGGGCCCTGCC
401	GATGATTAGTTCAGAGATA	402	TATCTCTGAACATATCATC

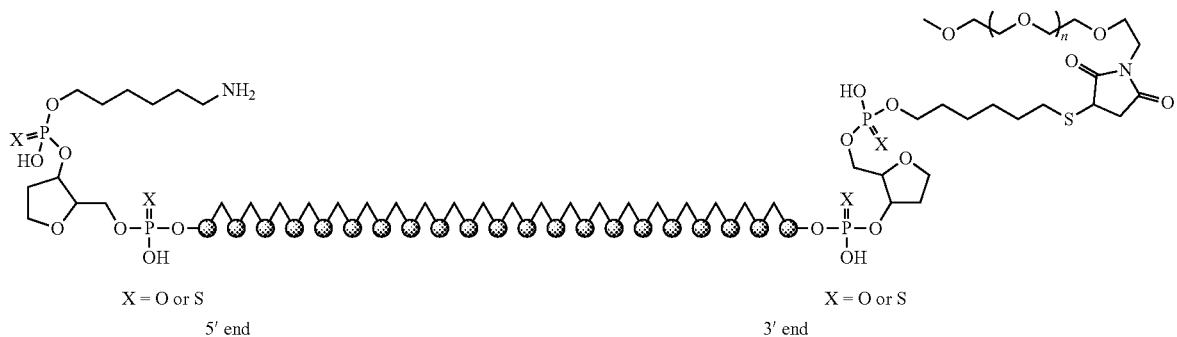
Example 2. siRNA Sequences and Synthesis

[0353] All siRNA single strands were fully assembled on solid phase using standard phosphoramidite chemistry and purified over HPLC. Purified single strands were duplexed to get the double stranded siRNA. All the siRNA passenger strand contains conjugation handles in different formats,

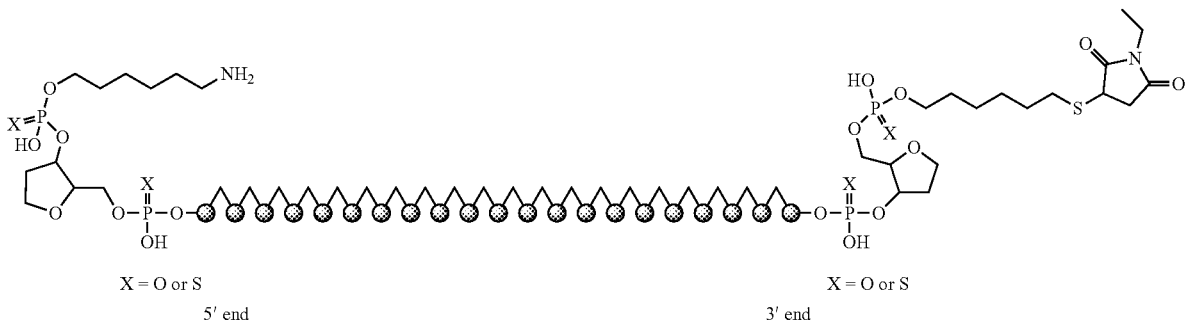
C_6-NH_2 and/or C_6-SH , one at each end of the strand. The conjugation handle or handles were connected to the siRNA passenger strand or siRNA guide strand via inverted abasic phosphodiester or phosphorothioate. Below are representative structures of the formats used in the in vivo experiments.



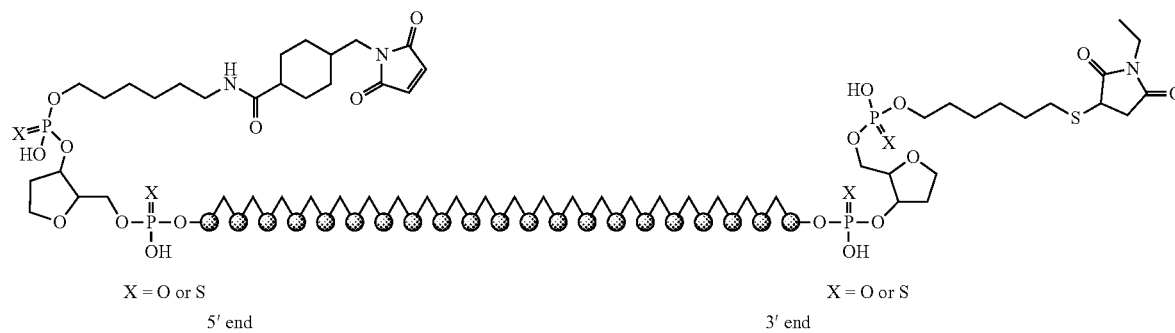
[0354] A representative structure of siRNA with C_6-NH_2 conjugation handle at the 5' end and C_6-SH at 3' end of the passenger strand or guide strand.



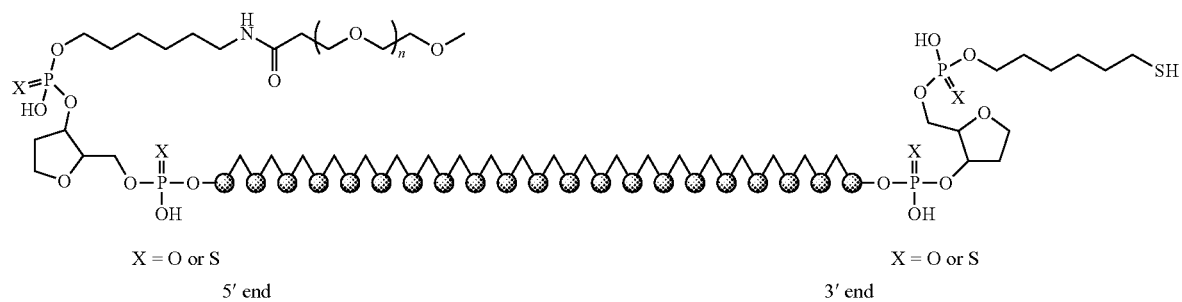
[0355] A representative structure of siRNA passenger strand or guide strand with C_6-NH_2 conjugation handle at the 5' end and C6-S-PEG at 3' end.



[0356] A representative structure of siRNA passenger strand or guide strand with C₆-NH₂ conjugation handle at the 5' end and C₆-S-NEM at 3' end.



[0357] A representative structure of siRNA passenger strand or guide strand with C₆-N-SMCC conjugation handle at the 5' end and C₆-S-NEM at 3' end.



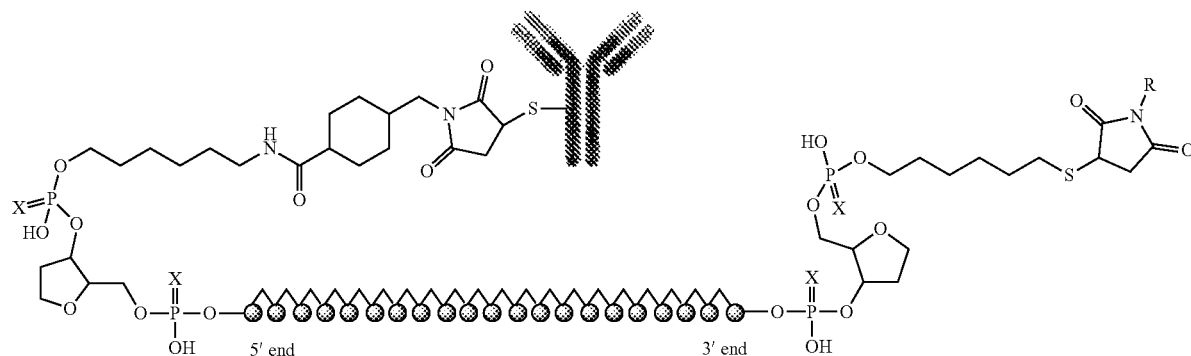
[0358] A representative structure of siRNA passenger strand or guide strand with PEG at the 5' end and C₆-SH at 3' end.



[0359] A representative structure of siRNA passenger strand or guide strand with C₆-S-NEM at the 5' end and C₆-NH₂ conjugation handle at 3' end.

Example 3. Conjugate Synthesis

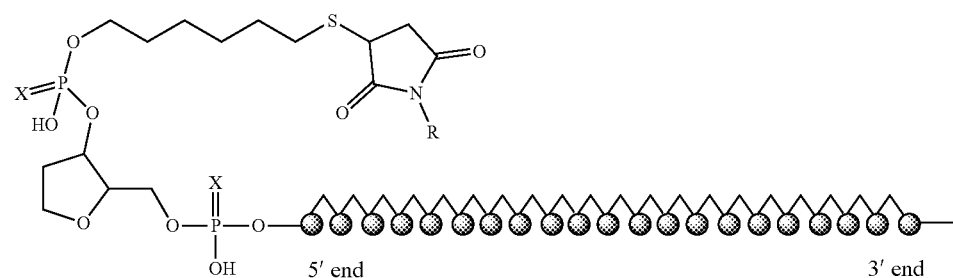
[0360] The following structures illustrate exemplary A-X₁-B-X₂-Y (Formula I) architectures described herein.



X = O or S
R = Ethyl or PEG 0.5 kDa to 10 kDa

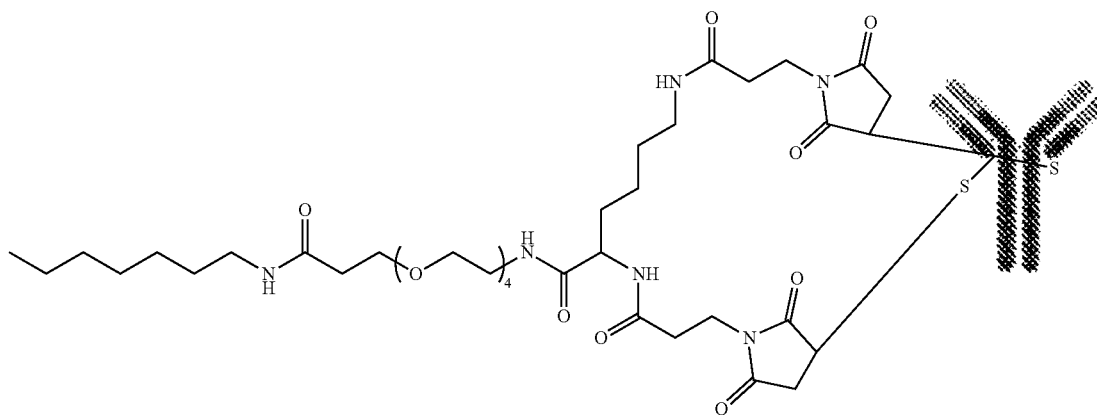
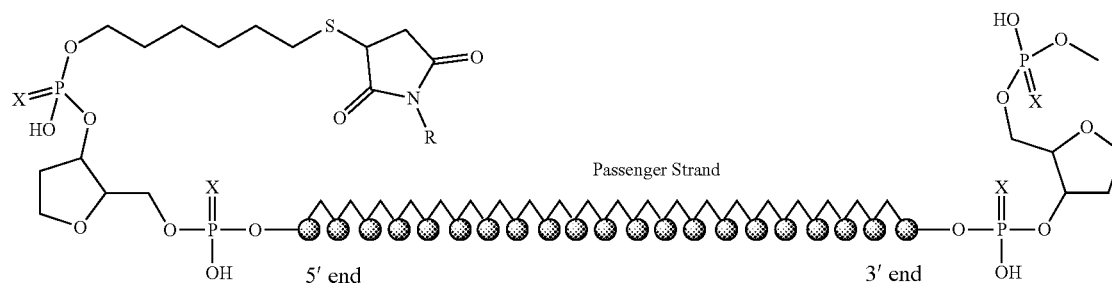
[0361] Architecture-1: Antibody-Cys-SMCC-5'-passenger strand. This conjugate was generated by antibody inter-chain

cysteine conjugation to maleimide (SMCC) at the 5' end of passenger strand.



X = O or S
R = Ethyl or PEG 0.5 kDa to 10kDa

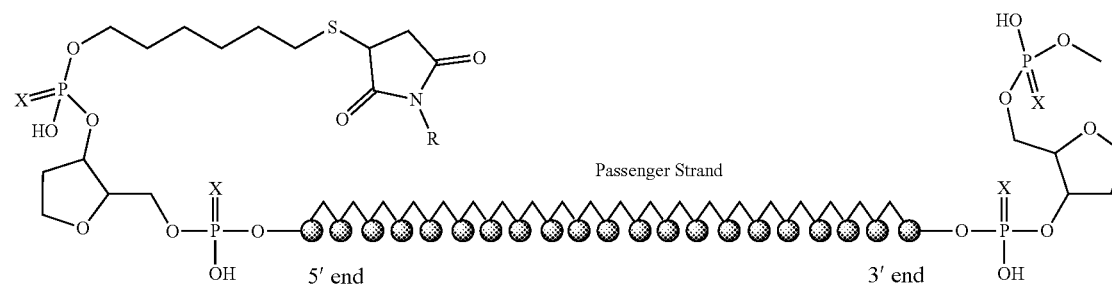
[0362] Architecture-2: Antibody-Cys-SMCC-3'-Passenger strand. This conjugate was generated by antibody inter-chain cysteine conjugation to maleimide (SMCC) at the 3' end of passenger strand.



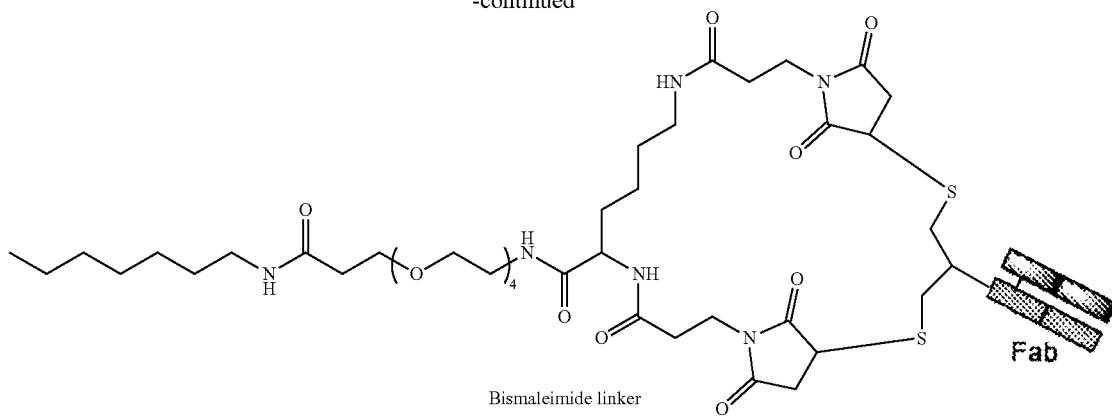
X = O or S
R = Ethyl or PEG 0.5 kDa to 10kDa

[0363] ASC Architecture-3: Antibody-Cys-bisMal-3'-Passenger strand. This conjugate was generated by antibody

inter-chain cysteine conjugation to bismaleimide (bisMal) linker at the 3' end of passenger strand.



-continued

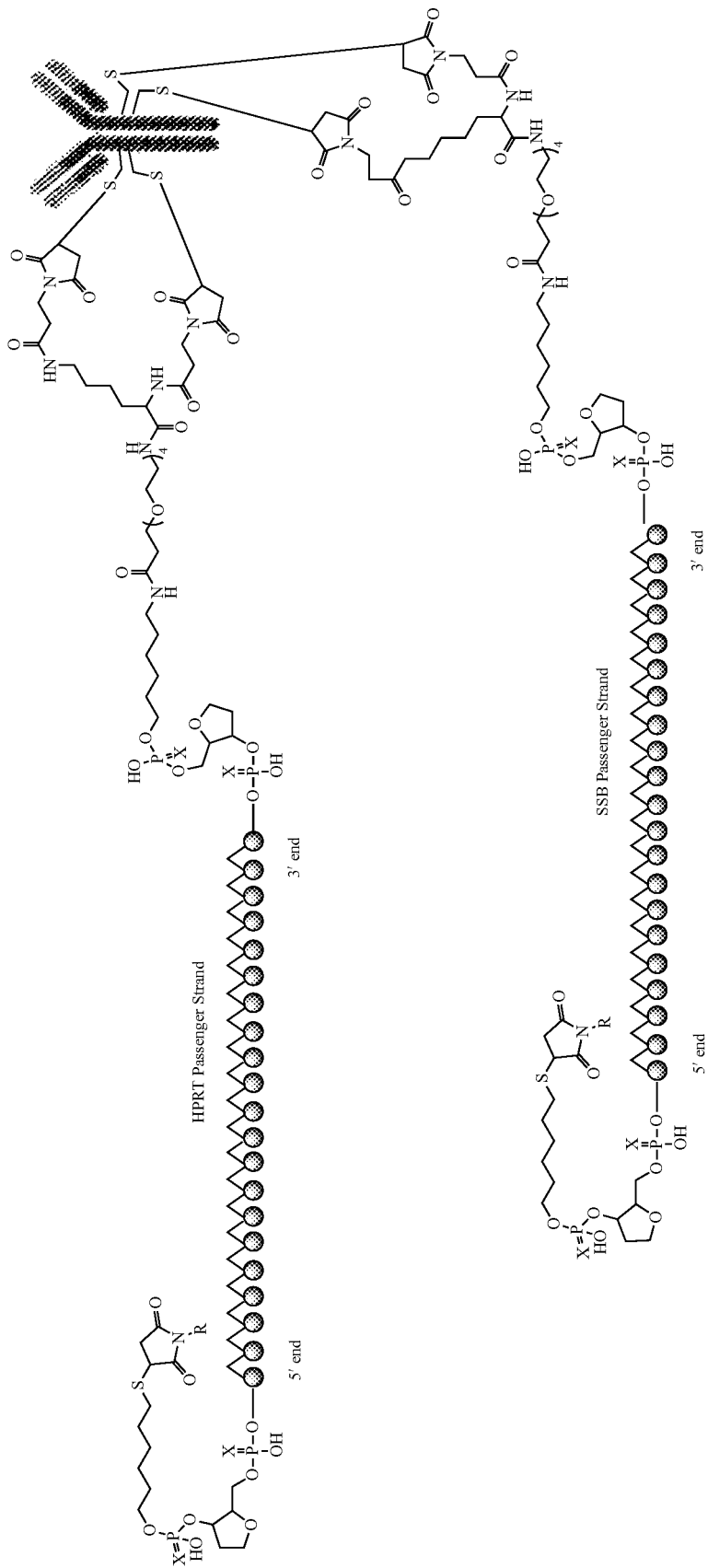


X = O or S

R = Ethyl or PEG 0.5 kDa to 10kDa

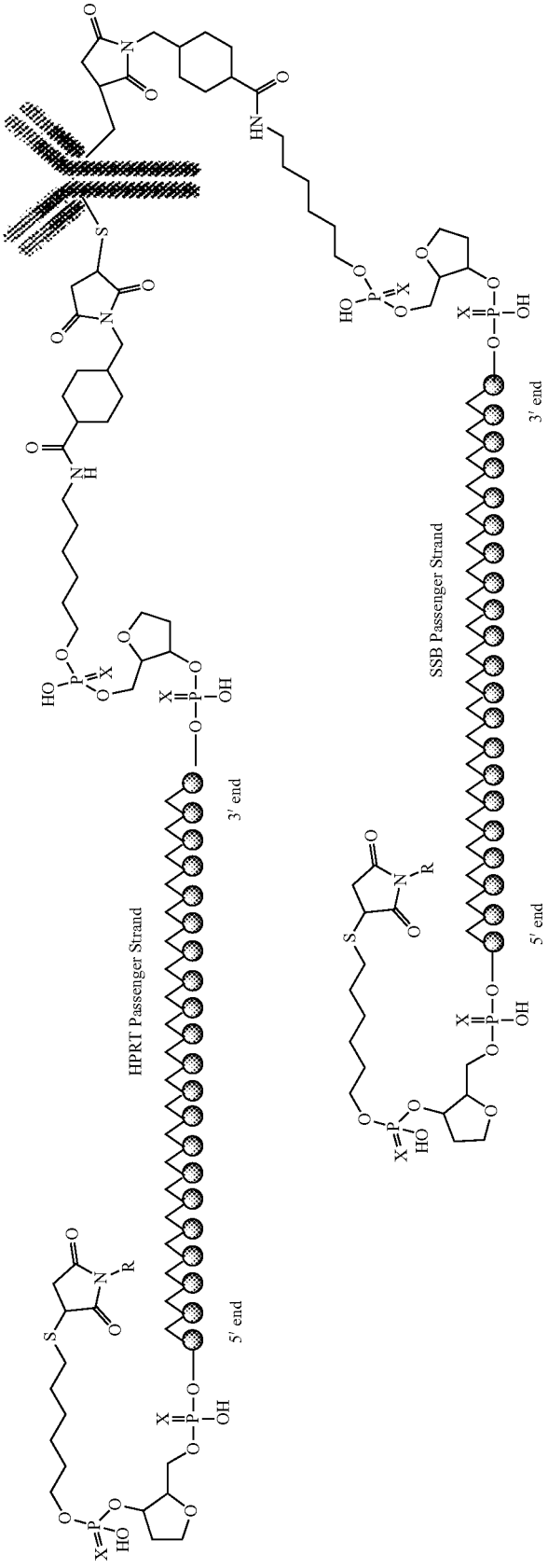
[0364] ASC Architecture-4: A model structure of the Fab-Cys-bisMal-3'-Passenger strand. This conjugate was gener-

ated by Fab inter-chain cysteine conjugation to bismaleimide (bisMal) linker at the 3' end of passenger strand.



X = O or S
 R = Ethyl or PEG 0.5 kDa to 10 kDa

[0365] ASC Architecture-5. A model structure of the antibody siRNA conjugate with two different siRNAs attached to one antibody molecule. This conjugate was generated by conjugating a mixture of SSB and HPRT siRNAs to the reduced mAb inter-chain cysteines to bismaleimide (bisMal) linker at the 3' end of passenger strand of each siRNA.



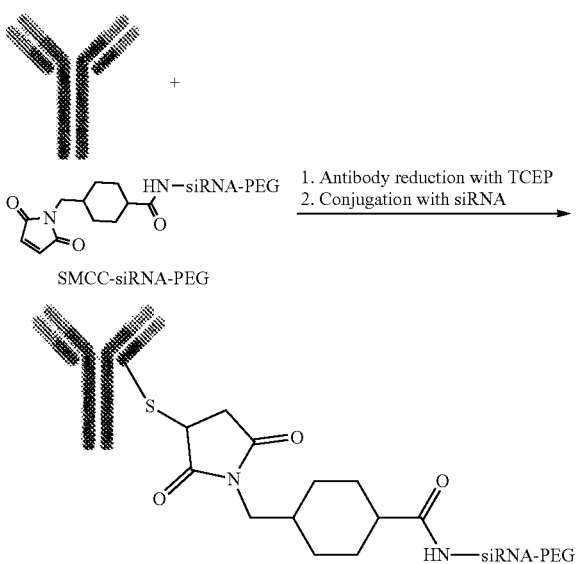
X = O or S
R = Ethyl/ or PEG 0.5 kDa to 10kDa

[0366] ASC Architecture-6: A model structure of the antibody siRNA conjugate with two different siRNAs attached. This conjugate was generated by conjugating a mixture of SSB and HPRT siRNAs to the reduced mAb inter-chain cysteines to maleimide (SMCC) linker at the 3' end of passenger strand of each siRNA.

Example 3.1 Antibody siRNA Conjugate Synthesis Using SMCC Linker

[0367]

Synthesis scheme-1: Antibody-Cys-SMCC-siRNA-PEG conjugates via antibody cysteine conjugation



Step 1: Antibody Interchain Disulfide Reduction with TCEP

[0368] Antibody was buffer exchanged with borax buffer (pH 8) and made up to 10 mg/ml concentration. To this solution, 2 equivalents of TCEP in water was added and rotated for 2 hours at RT. The resultant reaction mixture was buffer exchanged with pH 7.4 PBS containing 5 mM EDTA and added to a solution of SMCC-C6-siRNA or SMCC-C6-siRNA-C6-NHCO-PEG-XkDa (2 equivalents) (X=0.5 kDa to 10 kDa) in pH 7.4 PBS containing 5 mM EDTA at RT and rotated overnight. Analysis of the reaction mixture by analytical SAX column chromatography showed antibody siRNA conjugate along with unreacted antibody and siRNA.

Step 2: Purification

[0369] The crude reaction mixture was purified by AKTA explorer FPLC using anion exchange chromatography method-1 as described in Example 3.4. Fractions containing DAR1 and DAR>2 antibody-siRNA-PEG conjugates were separated, concentrated and buffer exchanged with pH 7.4 PBS.

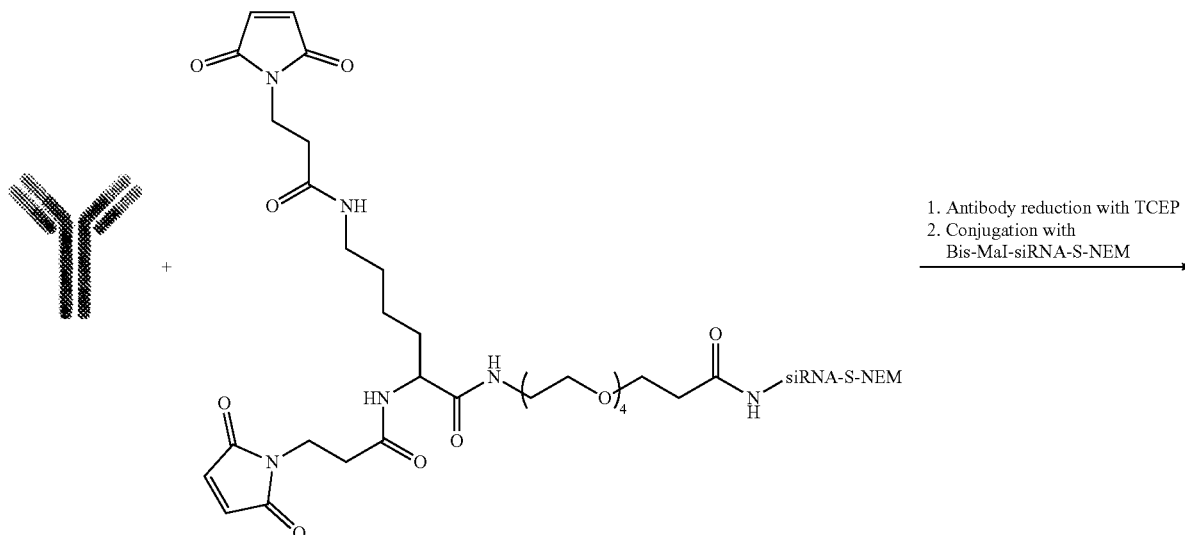
Step 3: Analysis of the Purified Conjugate

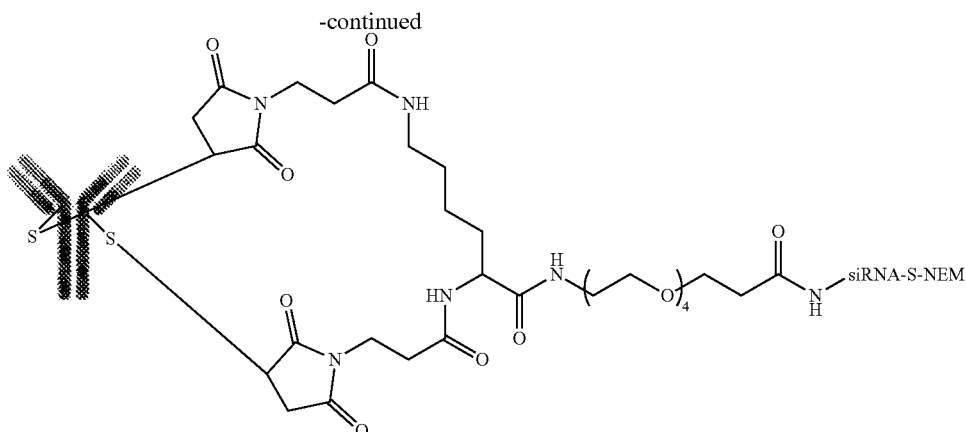
[0370] The isolated conjugates were characterized by SEC, SAX chromatography and SDS-PAGE. The purity of the conjugate was assessed by analytical HPLC using either anion exchange chromatography method-2 or anion exchange chromatography method-3. Both methods are described in Example 3.4. Isolated DAR1 conjugates are typically eluted at 9.0 ± 0.3 min on analytical SAX method and are greater than 90% pure. The typical DAR>2 cysteine conjugate contains more than 85% DAR2 and less than 15% DAR3.

Example 3.2. Antibody siRNA Conjugate Synthesis Using Bis-Maleimide (BisMal) Linker

[0371]

Synthesis scheme-2: Antibody-Cys-BisMal-siRNA-PEG conjugates.





Step 1: Antibody Reduction with TCEP

[0372] Antibody was buffer exchanged with borax buffer (pH 8) and made up to 5 mg/ml concentration. To this solution, 2 equivalents of TCEP in water was added and rotated for 2 hours at RT. The resultant reaction mixture was exchanged with pH 7.4 PBS containing 5 mM EDTA and added to a solution of BisMal-C6-siRNA-C6-S-NEM (2 equivalents) in pH 7.4 PBS containing 5 mM EDTA at RT and kept at 4° C. overnight. Analysis of the reaction mixture by analytical SAX column chromatography showed antibody siRNA conjugate along with unreacted antibody and siRNA.

Step 2: Purification

[0373] The crude reaction mixture was purified by AKTA explorer FPLC using anion exchange chromatography method-1. Fractions containing DAR1 and DAR2 antibody-siRNA conjugates were separated, concentrated and buffer exchanged with pH 7.4 PBS.

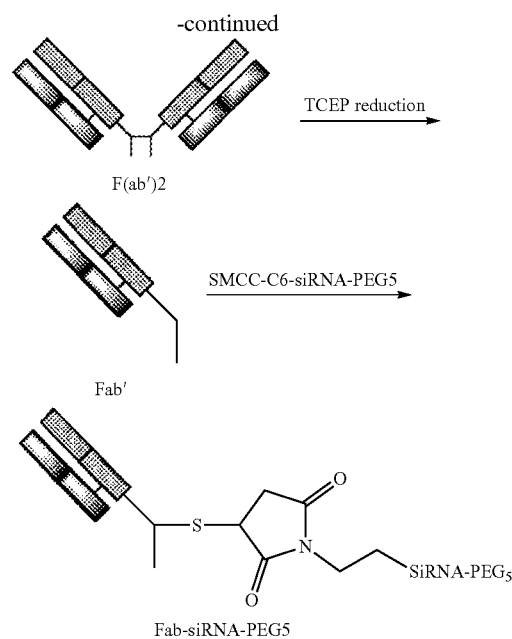
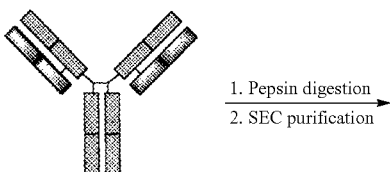
Step-3: Analysis of the Purified Conjugate

[0374] The isolated conjugates were characterized by either mass spec or SDS-PAGE. The purity of the conjugate was assessed by analytical HPLC using either anion exchange chromatography method-2 or 3 as well as size exclusion chromatography method-1.

Example 3.3. Fab' Generation from mAb and Conjugation to siRNA

[0375]

Scheme-3: Fab-siRNA-PEG5



Step 1: Antibody Digestion with Pepsin

[0376] Antibody was buffer exchanged with pH 4.0, 20 mM sodium acetate/acetic acid buffer and made up to 5 mg/ml concentration. Immobilized pepsin (Thermo Scientific, Prod #20343) was added and incubated for 3 hours at 37° C. The reaction mixture was filtered using 30 kDa MWCO Amicon spin filters and pH 7.4 PBS. The retentate was collected and purified using size exclusion chromatography to isolate F(ab')₂. The collected F(ab')₂ was then reduced by 10 equivalents of TCEP and conjugated with SMCC-C₆-siRNA-PEG₅ at room temperature in pH 7.4 PBS. Analysis of reaction mixture on SAX chromatography showed Fab-siRNA conjugate along with unreacted Fab and siRNA-PEG.

Step 2: Purification

[0377] The crude reaction mixture was purified by AKTA explorer FPLC using anion exchange chromatography

method-1. Fractions containing DAR1 and DAR2 Fab-siRNA conjugates were separated, concentrated and buffer exchanged with pH 7.4 PBS.

Step-3: Analysis of the Purified Conjugate

[0378] The characterization and purity of the isolated conjugate was assessed by analytical HPLC using anion exchange chromatography method-2 or 3 as well as by SEC method-1.

Example 3.4. Purification and Analytical Methods

[0379] Anion Exchange Chromatography Method (SAX)-1.

- [0380]** 1. Column: Tosoh Bioscience, TSKGel SuperQ-5PW, 21.5 mm ID×15 cm, 13 μm
[0381] 2. Solvent A: 20 mM TRIS buffer, pH 8.0; Solvent B: 20 mM TRIS, 1.5 M NaCl, pH 8.0; Flow Rate: 6.0 ml/min
[0382] 3. Gradient:

a.	% A	% B	Column Volume
b.	100	0	1.00
c.	60	40	18.00
d.	40	60	2.00
e.	40	60	5.00
f.	0	100	2.00
g.	100	0	2.00

[0383] Anion Exchange Chromatography (SAX) Method-2

- [0384]** 1. Column: Thermo Scientific, ProPac™ SAX-10, Bio LC™, 4×250 mm
[0385] 2. Solvent A: 80% 10 mM TRIS pH 8, 20% ethanol; Solvent B: 80% 10 mM TRIS pH 8, 20% ethanol, 1.5 M NaCl; Flow Rate: 0.75 ml/min
[0386] 3. Gradient:

a.	Time	% A	% B
b.	0.0	90	10
c.	3.00	90	10
d.	11.00	40	60
e.	23.00	40	60
f.	25.00	90	10
g.	30.00	90	10

[0387] Anion Exchange Chromatography (SAX) Method-3

- [0388]** 1. Column: Thermo Scientific, ProPac™ SAX-10, Bio LC™, 4×250 mm
[0389] 2. Solvent A: 80% 10 mM TRIS pH 8, 20% ethanol; Solvent B: 80% 10 mM TRIS pH 8, 20% ethanol, 1.5 M NaCl
[0390] 3. Flow Rate; 0.75 ml/min
[0391] 4. Gradient:

a.	Time	% A	% B
b.	0.0	90	10
c.	3.00	90	10
d.	11.00	40	60
e.	13.00	40	60

-continued

a.	Time	% A	% B
f.	15.00	90	10
g.	20.00	90	10

[0392] Size Exclusion Chromatography (SEC) Method-1

- [0393]** 1. Column: TOSOH Biosciences, TSKgelG3000SW XL, 7.8×300 mm, 5 μM
[0394] 2. Mobile phase: 150 mM phosphate buffer
[0395] 3. Flow Rate: 1.0 ml/min for 15 mins

Example 3.5. Antibody siRNA Conjugate Synthesis Using Bis-Maleimide (BisMal) Linker

Step 1: Antibody Reduction with TCEP

[0396] Antibody was buffer exchanged with 25 mM borate buffer (pH 8) with 1 mM DTPA and made up to 10 mg/ml concentration. To this solution, 4 equivalents of TCEP in the same borate buffer were added and incubated for 2 hours at 37° C. The resultant reaction mixture was combined with a solution of BisMal-siRNA (1.25 equivalents) in pH 6.0 10 mM acetate buffer at RT and kept at 4° C. overnight. Analysis of the reaction mixture by analytical SAX column chromatography showed antibody siRNA conjugate along with unreacted antibody and siRNA. The reaction mixture was treated with 10 EQ of N-ethylmaleimide (in DMSO at 10 mg/mL) to cap any remaining free cysteine residues.

Step 2: Purification

[0397] The crude reaction mixture was purified by AKTA Pure FPLC using anion exchange chromatography (SAX) method-1. Fractions containing DAR1 and DAR2 antibody-siRNA conjugates were isolated, concentrated and buffer exchanged with pH 7.4 PBS.

[0398] Anion Exchange Chromatography Method (SAX)-1.

- [0399]** Column: Tosoh Bioscience, TSKGel SuperQ-5PW, 21.5 mm ID×15 cm, 13 μm
[0400] Solvent A: 20 mM TRIS buffer, pH 8.0; Solvent B: 20 mM TRIS, 1.5 M NaCl, pH 8.0; Flow Rate: 6.0 ml/min
[0401] Gradient:

a.	% A	% B	Column Volume
b.	100	0	1
c.	81	19	0.5
d.	50	50	13
e.	40	60	0.5
f.	0	100	0.5
g.	100	0	2

[0402] Anion Exchange Chromatography (SAX) Method-2

- [0403]** Column: Thermo Scientific, ProPac™ SAX-10, Bio LC™, 4×250 mm
[0404] Solvent A: 80% 10 mM TRIS pH 8, 20% ethanol; Solvent B: 80% 10 mM TRIS pH 8, 20% ethanol, 1.5 M NaCl; Flow Rate: 0.75 ml/min

[0405] Gradient:

a.	Time	% A	% B
b.	0.0	90	10
c.	3.00	90	10
d.	11.00	40	60
e.	14.00	40	60
f.	15.00	20	80
g.	16.00	90	10
h.	20.00	90	10

Example 4. Expression Profile of DUX4 in Myonuclei

[0406] Myotubes derived from a healthy individual and FSHD patient were evaluated for DUX4 expression. As shown in FIG. 4, myotubes were immunostained to detect DUX4 expression. Muscle cells' nuclei and cytoplasm were immunostained by labeling DAPI (4',6-diamidino-2-phenylindole) and troponin T. As shown, DUX4 expression could be detected in low and sporadic manner—in less than 1% of myonuclei—indicating that detecting of DUX4 expression directly from the cell can be challenging in determining the effect of DUX4 siRNA activity.

Example 5. Expression Profiles of DUX4-Dependent Marker Genes in FSHD Donor Muscle Cells with DUX4 siRNA Treatment

[0407] Two DUX4 siRNAs (siDUX4-1 and siDUX4-4 are disclosed in Geng L N et al. *Dev. Cell*, 2012) were used to treat the diseased muscle cells (FSHD donor muscle cells), and RNA expression level of five DUX4-dependent biomarker genes were quantitated, as shown in bar graphs in FIG. 5. As shown, both siDUX4-1 and siDUX4-4 substantially reduced the expression of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, and LEUTX compared to the baseline (100%). More specifically, siDUX4-4 reduced the expression of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, and LEUTX at least ~75% compared to the baseline (100%). DUX4-target genes as biomarkers were sensitive to measure siRNA-mediated downregulation of DUX4.

Example 6. DUX4 siRNA-Mediated Reduction of 5 DUX4-Target Biomarker Gene Expressions and a FSHD Composite of DUX4-Target Biomarker Genes in Cultured FSHD Primary Myotubes

[0408] FSHD1 patient-derived primary myoblasts (MB06) were used to validate the FSHD composite as a reliable surrogate biomarker to assess DUX4 siRNA activity with the published 2 DUX4 siRNAs, siDUX4-1 and siDUX4-4 (Geng L N et al, *Dev. Cell*, 2012) in a dose dependent concentration. FSHD primary myoblasts (MB06 (FSHD1)) were grown in recommended media. Prior to seeding, 96-well tissue culture plates (Costar) were coated with 50 μ L of 1% Matrigel per well for at least 2 hours at 37° C., and washed 2 \times with PBS. After coating, myoblasts were seeded in quadruplicate at 4000 cells/well without antibiotics and maintained 24h prior to transfection. On the day of transfection, the DUX4-4 siRNA was formulated with commercially available transfection reagent Lipofectamine RNAiMAX (Life Technologies) and OptiMEM (Life Technologies) according to the manufacturer's "forward transfection" instructions. DUX4-4 siRNA was synthesized by Integrated DNA Technologies (IDT). Myoblasts were trans-

ected with DUX4-4 siRNA at a high concentration of 25 nM with 9-fold serial dilutions. 24 hours post transfection, myogenic differentiation was induced with 15% KOSR-containing differentiation medium. Myotubes were collected in Trizol 4 days after inducing differentiation and stored at -80°C until processing. RNA isolation was performed using Direct-zol-96 RNA isolation kit (Zymo) according to the manufacturer's instructions. 100-500 ng of purified RNA was converted to cDNA using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) using SimpliAmp Thermal Cycler (Applied Biosystems). cDNA was analyzed by qPCR using TaqMan Fast Universal Master Mix II (Thermo Fisher) and TaqMan probes (Thermo Fisher) in duplicates, using QuantStudio 6 or 7 Flex Real-Time PCR instruments (Applied Biosystems). Data were analyzed by QuantStudio™ Real-Time PCR Software v1.3 (Applied Biosystems). The expression levels of 5 DUX4-target genes were evaluated: MBD3L2, ZSCAN4, LEUTX, KHDC1L, and TRIM43. DUX4-target gene expression was normalized to a composite of two reference genes: AHSA1 and RPL27. The percentage of target mRNA expression was determined relative to mock treated cells by using the $2^{-\Delta\Delta Ct}$ method (Livak and Schmittgen, *Methods* 2001). FIG. 6A-B show DUX4 siRNA-mediated reduction of 5 DUX4-target biomarker gene expressions in cultured FSHD primary myotubes. DUX4 siRNA reduced the expression of 5 individual DUX4-target biomarker genes (MBD3L2, ZSCAN4, LEUTX, KHDC1L, and TRIM43) (FIG. 6A) or as a FSHD composite of the 5 DUX4-target biomarker genes (FIG. 6B) in cultured FSHD primary myotubes.

Example 7. DUX4 siRNA Library Screening—First Round at 2 Concentrations (10 and 0.5 nM) in MB02 and MB06

[0409] In this example, 70 DUX4 siRNAs were screened for their activity in two FSHD primary myoblast cell lines (MB02 (FSHD1) and MB06 (FSHD1)) to identify more desirable siRNA candidates. Cells were plated at a density of 4,000 cells/well (MW96) and then transfected in four replicates with DUX4 siRNAs, as well as a tool siRNA as control. Transfection was performed 24 hours after plating at 10 nM concentration. Myogenic differentiation was induced 2 days after plating (24 hours after transfection) with 15% KOSR (in DMEM/F-12) medium. Samples were harvested 3 or 4 days after inducing differentiation, depending on the cell line. DUX4-downstream target gene expression was evaluated by RT-qPCR (normalized to a composite AHSA1 and RPL27 housekeeping gene expression value). Data shown in this example are represented as mean FSHD Composite-/+SEM. N=4.

[0410] FIG. 7 shows a bar graph of assessment of myotubes differentiation and viability at 10 nM concentration of siDUX4 by monitoring ACTA1 expression in MB02 (FSHD1) and MB06 (FSHD1) cell lines.

[0411] FIG. 8 shows a bar graph of screening for activity at 10 nM Concentration of 70 DUX4 siRNAs by measuring FSHD composite expression (Calculations of the FSHD composite: $Dct=(Av. ct 4 DUX4 target genes)-(Av. ct 2 HKGs)$, $DDct=Dct (siDUX4)-Dct (mock)$, $Composite=2^{-DDct*100(\%)}$).

[0412] FIG. 9 shows a bar graph of screening for activity at 0.5 nM Concentration of 70 DUX4 siRNAs by measuring FSHD composite expression. As used herein. FSHD Com-

posite is made of 4 DUX4-target genes: MBD3L29 ZSCAN4, LEUTX, KHDC1L. As shown in Table 15, down-regulation of FSHD composite expression is well correlated with downregulation of individual genes in the composite

when normalized to HKG composite (AHS1, RPL27) (n=4), indicating that the effective downregulation of FSHD composite expression is a good indicator to DUX4 siRNA potency.

TABLE 15

siRNA	MB02							MB06
	FSHD Composite	KHDC11	LEUTX	MDB3L2	ZSCAN4	AHS1	RPI27	FSHD Composite
11	31.75	32.33	27.01	47.47	30.27	109.58	91.38	16.09
57	25.85	22.62	27.70	42.22	20.85	97.29	103.31	14.22
58	9.78	12.44	13.10	5.88	7.11	97.37	103.29	4.10
59	43.49	44.17	43.50	45.55	45.97	105.40	94.78	28.22
60	58.45	59.45	55.13	69.75	57.17	94.97	105.61	140.69
61	6.34	7.32	2.83	11.18	9.93	90.50	113.77	1.73
62	15.44	18.56	12.97	25.33	12.82	100.38	102.07	20.45
63	13.73	29.72	11.40	14.50	10.07	85.09	118.35	17.87
77	37.74	32.95	30.95	47.38	45.61	94.54	105.59	75.08
78	72.97	59.09	58.98	102.78	83.09	100.39	100.53	106.34
79	19.50	12.62	19.45	34.83	24.75	108.94	95.53	5.72
99	22.26	16.41	19.77	35.04	25.06	92.52	109.14	35.72
102	48.17	39.31	49.89	65.85	45.69	101.19	100.20	44.10
137	17.49	14.10	11.02	25.26	31.37	93.65	107.00	17.65
160	201.88	205.52	215.56	241.34	167.58	97.09	103.95	300.78
162	61.62	51.74	58.79	91.54	57.24	105.98	93.58	45.68
163	122.38	115.49	111.83	111.99	154.49	88.53	113.03	79.05
231	91.73	95.05	89.58	106.78	91.32	97.74	102.50	337.97
232	23.56	25.81	22.38	33.70	17.65	102.82	98.35	12.55
274	14.70	12.58	7.62	26.42	21.88	95.39	106.34	34.53
276	355.14	295.05	459.25	349.12	397.99	104.97	96.57	319.52
277	37.91	43.98	41.85	40.48	38.05	108.35	94.03	18.43
285	86.15	108.25	75.54	78.48	98.14	88.18	114.79	65.05
287	339.10	407.15	355.95	331.14	282.13	99.11	101.55	239.05
292	74.54	55.24	70.23	99.22	71.01	99.83	100.24	141.85
293	103.15	93.51	103.54	114.07	115.31	95.28	104.03	55.65
294	104.91	113.05	114.54	112.24	92.48	92.28	108.55	147.19
335	12.62	12.47	13.75	15.54	14.57	100.38	100.54	1.77
289	101.16	143.98	74.83	103.37	105.53	91.50	110.54	87.13
524	10.70	7.90	5.81	18.87	20.05	102.71	97.55	11.57
525	41.37	44.14	45.56	39.27	41.85	100.52	100.49	147.51
672	1105.70	976.91	1558.44	1316.38	778.03	102.53	97.86	875.88
679	126.54	165.55	124.45	112.83	118.55	84.77	118.50	111.13
704	93.68	93.39	94.12	118.54	85.98	100.74	100.94	382.40
705	52.22	52.53	39.24	70.91	49.46	100.96	99.96	37.85
708	19.24	27.41	17.79	21.23	14.34	105.74	95.27	13.86
882	65.40	41.13	61.93	118.03	64.59	108.83	93.30	95.03
884	34.58	28.82	25.19	51.92	42.17	106.64	95.66	25.97
893	15.06	12.73	13.13	23.42	14.15	80.16	124.98	25.57
1045	33.86	28.20	32.38	42.01	42.10	102.03	99.58	72.20
1132	3.20	4.19	1.89	42.6	4.64	92.42	110.66	2.17
1134	41.73	31.74	27.87	62.98	58.37	97.67	103.39	165.18
1158	7.01	6.51	4.48	13.33	9.47	91.29	109.76	8.01
1159	226.21	152.73	154.74	292.83	401.40	82.15	126.63	525.79
1163	11.52	15.00	8.01	15.75	10.55	94.55	106.71	0.62
1236	4.22	3.32	1.94	8.35	8.47	82.34	121.73	1.85
1237	32.87	31.02	25.17	43.61	38.79	97.35	102.99	18.02
1238	24.43	25.07	19.03	35.16	24.46	105.02	95.44	29.53
1284	90.11	83.12	84.62	106.45	100.99	98.75	106.13	26.55
1290	104.36	97.53	102.02	118.57	109.73	100.22	101.46	335.73
1294	108.34	91.38	115.59	177.24	78.03	114.67	88.47	210.94
1295	60.35	60.16	43.80	96.21	55.94	69.18	145.68	26.36
1315	92.84	85.02	96.47	111.78	83.44	107.21	93.35	132.47
1316	82.53	68.66	62.91	154.83	71.10	97.30	103.65	170.76
1317	104.92	105.43	101.20	112.07	112.09	97.95	105.07	155.72
1321	23.72	20.71	13.75	44.87	29.79	87.40	115.65	30.38
1340	13.06	14.55	14.52	14.04	12.12	76.27	131.90	12.24
1350	207.49	155.67	224.45	254.19	222.09	103.71	96.95	108.59
1351	2217.65	1074.92	2732.04	3210.96	2752.93	135.49	75.80	556.04
1539	85.20	76.82	87.54	121.01	73.71	98.65	102.96	174.37
1540	27.76	27.63	21.74	39.45	27.56	99.84	100.4	6.96
1541	27.45	23.47	21.75	36.77	33.40	94.71	106.55	19.68
1610	28.54	14.04	21.45	56.20	41.60	102.33	98.02	26.04
1611	31.12	23.09	26.42	59.28	27.96	96.38	104.00	148.02
1612	55.31	46.84	46.05	91.02	53.05	104.00	97.07	166.82
1613	5.18	6.53	1.37	8.42	9.92	96.50	106.13	13.55

TABLE 15-continued

1615	39.81	36.59	35.01	62.94	35.85	103.77	97.50	15.05
1616	31.13	28.01	32.41	33.99	31.93	94.67	106.96	24.95
1619	16.06	11.42	7.09	38.40	25.85	96.42	104.14	19.69
1632	17.02	21.17	23.00	26.39	8.73	109.10	92.79	4.83
MB06								
	siRNA	KHDC11	LEUTX	MBD3L2	ZSCAN4	AHSA1	RPI27	
	11	8.38	11.09	23.82	33.31	114.05	90.97	
	57	12.15	10.51	18.81	19.54	89.28	115.02	
	58	2.57	2.37	6.05	11.34	10.19	105.55	
	59	22.48	29.71	33.29	32.50	117.04	88.15	
	60	122.45	142.62	155.90	150.70	116.93	4.15	
	61	1.57	1.08	1.78	4.58	9.85	114.58	
	62	10.45	15.63	37.90	32.54	101.13	102.58	
	63	21.42	13.53	24.40	16.06	83.35	122.84	
	77	53.88	58.53	78.07	112.37	111.85	93.58	
	78	79.97	85.79	123.98	154.02	103.95	101.34	
	79	7.19	3.78	5.70	8.23	99.32	104.82	
	99	25.35	26.35	40.43	63.61	99.65	104.80	
	102	57.01	39.54	42.83	40.52	90.72	119.87	
	137	1.24	12.00	21.07	33.17	98.95	105.09	
	160	306.57	304.41	294.44	312.89	108.55	100.20	
	162	29.38	37.70	55.89	73.25	105.10	97.57	
	163	63.62	72.05	62.17	144.47	95.43	109.30	
	231	283.17	379.63	352.81	354.24	115.95	92.45	
	232	11.16	9.33	15.35	17.15	92.25	109.99	
	274	26.94	29.25	37.69	50.61	103.83	99.85	
	276	337.69	319.51	228.18	44.51	199.52	110.28	
	277	17.38	16.75	19.54	22.05	100.75	102.23	
	285	53.72	56.52	72.14	71.55	102.87	103.35	
	287	253.18	231.21	228.18	257.25	101.75	102.15	
	292	143.88	135.19	159.14	135.01	103.00	105.57	
	293	40.83	48.59	71.53	70.82	103.57	100.30	
	294	163.93	152.23	129.50	154.54	104.25	104.91	
	335	1.85	0.74	2.24	3.69	105.87	100.27	
	289	87.19	61.30	80.98	139.82	97.28	110.00	
	524	8.50	7.01	13.83	22.05	125.94	84.71	
	525	131.00	168.52	148.43	149.22	115.00	89.05	
	672	932.45	950.25	747.57	916.32	95.33	105.59	
	679	89.15	108.25	119.11	139.93	108.59	99.35	
	704	345.98	392.90	385.90	415.94	110.04	98.08	
	705	40.55	22.82	47.40	50.42	95.14	108.51	
	708	12.61	8.91	21.99	16.45	110.19	98.33	
	882	51.51	92.26	137.90	135.15	126.73	85.08	
	884	22.07	25.24	23.84	38.18	121.69	88.93	
	893	22.57	17.56	18.86	61.47	74.41	151.83	
	1045	55.02	62.24	73.95	110.04	112.74	93.00	
	1132	1.38	1.22	2.33	4.89	110.80	95.16	
	1134	124.57	138.47	238.72	194.16	120.19	96.87	
	1158	6.27	3.33	14.17	16.01	103.69	100.97	
	1159	246.31	419.47	961.82	840.11	109.42	94.92	
	1163	0.71	0.24	1.16	1.49	114.57	93.45	
	1236	1.56	0.70	2.59	4.72	83.65	125.55	
	1237	15.99	12.24	19.83	28.35	86.15	127.14	
	1238	23.79	22.54	35.10	43.41	106.57	101.82	
	1284	26.17	21.71	21.91	47.85	105.06	107.66	
	1290	277.05	410.94	346.25	336.63	129.53	81.28	
	1294	212.54	213.33	192.41	237.66	104.07	108.48	
	1295	19.44	20.39	39.85	33.69	80.55	134.12	
	1315	131.69	120.09	124.25	162.31	102.73	107.96	
	1316	141.70	168.39	207.31	175.30	116.86	93.87	
	1317	136.41	146.45	192.41	163.46	116.80	89.59	
	1321	22.32	20.48	43.92	44.59	91.46	115.30	
	1340	16.78	10.49	8.35	17.48	80.76	135.39	
	1350	73.33	116.32	128.51	130.28	111.71	94.61	
	1351	409.02	572.93	604.80	690.63	124.43	89.12	
	1539	162.38	150.76	180.05	217.16	105.72	100.85	
	1540	10.19	3.38	8.01	9.77	95.47	111.96	
	1541	13.08	13.65	27.71	34.20	104.27	100.39	
	1610	14.84	20.65	28.45	59.48	111.99	98.08	
	1611	126.75	169.36	178.77	128.62	115.44	90.38	
	1612	149.98	188.56	161.52	174.12	123.98	87.12	
	1613	10.97	6.06	22.26	24.00	110.12	94.54	
	1615	10.29	8.06	20.20	34.44	98.28	107.83	
	1616	15.42	15.50	31.87	59.94	104.72	99.75	

TABLE 15-continued

1619	15.64	10.91	33.63	30.66	103.27	106.14
1632	6.04	2.20	7.24	6.80	101.92	104.27

[0413] As shown in FIG. 10, from the DUX4 siRNA library with 70 siRNA candidates 37 candidates were eliminated that have lower than 70% KD in at least one cell lines at 10 nM. Then, 3 additional siRNA candidates were eliminated that resulted in ACTA1 expression less than 70% in both cell lines. Then, 2 additional siRNA candidates with null activity (<10% KD) at 0.5 nM in both cell lines were eliminated, resulting in total 28 siRNA candidates left for the next screening process. Table 16 lists such selected 28 DUX4 siRNAs and the downregulation of FSHD composite expression in two cell lines at the concentration of 10 nM and 0.5 nM of the selected 28 DUX4 siRNAs (also shown as bar graphs in FIGS. 11A and 11B).

TABLE 16

siRNA	FSHD Composite (% Mock)			
	MB02—10 nM	MB02—0.5 nM	MB06—10 nM	MB06—0.5 nM
11	31.76	51.87	16.09	76.24
57	25.86	64.82	14.22	38.21
58	9.78	40.95	4.10	88.52
61	6.34	34.34	1.73	48.20
62	15.44	45.95	20.46	85.52
63	13.73	52.64	17.87	79.18
79	19.50	56.01	5.72	71.70
99	22.26	63.90	35.72	91.67
137	17.49	39.13	17.66	71.37
277	37.91	76.29	18.43	107.75
336	12.62	31.51	1.77	43.22
524	10.70	53.98	11.57	73.00
708	19.24	73.21	13.86	72.29
1132	3.20	59.37	2.17	66.00
1158	7.01	30.58	8.01	5440
1163	11.52	48.46	0.62	37.70
1236	4.22	25.00	1.85	16.55
1237	32.87	99.25	18.02	47.65
1238	24.43	60.92	29.53	82.40
1340	13.06	38.81	12.24	47.63
1540	27.76	17.63	6.96	17.57
1541	27.45	34.55	19.68	70.70
1610	28.54	50.65	26.04	76.91
1613	5.18	18.30	13.55	39.25
1615	39.81	45.49	15.05	50.57
1616	31.13	37.63	24.95	32.25
1619	16.06	42.95	19.69	49.95
1632	17.02	20.07	4.83	37.10

[0414] Databases of human polymorphisms are not reliable in repeats and it is possible that polymorphic positions may be missed. Thus, in this round of selection, siRNAs that show poor performance in one of two myoblast cell lines were eliminated for a purpose of validating that selected

DUX4 siRNAs are active in a variety of FSHD-patient derived myoblasts. FIG. 12 shows distribution of 70 siRNAs by their efficacies of downregulating FSHD composite in two myoblast cell lines. KD correlation analysis identified ~10% of DUX4 siRNAs that worked only in one of the two FSHD primary myoblast cell lines used in the full library screening.

Example 8. DUX4 siRNA Library Screening—Second Round at 10 nM in Four Different Patient-Derived Primary Myoblast Cell Lines

[0415] In this example, a total of 9 high quality FSHD patient-derived primary myoblast cell lines (6 FSHD1, 3 FSHD2) were used. Conditions that allow reliable detection of DUX4 target gene expression in FSHD myotubes in-house were established by culturing the cells in Differentiation medium (15% KOSR in DMEM/F-12). Time-point was selected specifically for each cell line. All 9 FSHD cell lines showed a concentration-dependent response to a tool DUX4 siRNA.

[0416] FIG. 13 shows a bar graph of ACTA1 expression levels in four different patient-derived primary myoblast cell lines (MB01, MB05, MB11, MB12). Most of the top 28 DUX4 siRNAs did not effect ACTA1 expression levels in these cell lines, while a few siRNAs showed more than 30% reduction in ACTA1 expression levels in the additional 4 FSHD primary cell lines tested (8 in MB11, 3 in MB05, 3 in MB12, and none in MB01). In addition, as shown in FIG. 14, the top 28 DUX4 siRNAs showed activity in all four additional FSHD primary cell lines. Several siRNAs showed more than 75% KD in three lines: MB05, MB11, MB12. KD levels were overall lower in MB01. FIG. 15 shows the top 28 DUX4 siRNAs' activity at 10 nM concentration in all FSHD cell lines (MB01, MB02, MB05, MB06, MB11, MB12).

[0417] Top 14 DUX4 siRNAs were selected from top 28 DUX4 siRNAs. Selection of such top 14 DUX4 siRNAs were i) siRNAs that showed no or minimal cell toxicity (visual identification and evaluation of ACTA1 expression levels), and ii) siRNAs that displayed the best activity at both 10 nM and 0.5 nM concentrations. Table 17 lists the top 14 DUX4 siRNAs and downregulation of FSHD composite expression in six primary FSHD cell lines (MB01, MB02, MB05, MB06, MB11, MB12) at the concentration of 10 nM and 0.5 nM of the selected 14 DUX4 siRNAs, and downregulation of ACTA1 expression in six primary FSHD cell lines at the concentration of 10 nM. Table 18 lists the top 14 DUX4 siRNAs and downregulation of FSHD composite expression in all 9 FSHD primary myotubes.

TABLE 17

siRNA	FSHD Composite (% Mock)						ACTA 1 (% Mock)							
	10 nM			0.5 nM			10 nM							
	MB01	MB02	MB05	MB06	MB11	MB12	MB02	MB06	MB01	MB02	MB05	MB06	MB11	MB12
11	43.10	31.76	15.02	16.09	2.66	13.06	51.87	76.24	182.43	149.99	114.72	134.18	74.18	123.86
57	60.89	25.86	16.05	14.22	29.01	43.75	64.82	38.21	134.81	133.87	77.42	136.08	101.53	122.19

TABLE 17-continued

siRNA	FSHD Composite (% Mock)						ACTA 1 (% Mock)							
	10 nM			0.5 nM			10 nM							
	MB01	MB02	MB05	MB06	MB11	MB12	MB02	MB06	MB01	MB02	MB05	MB06	MB11	MB12
58	47.60	9.78	8.74	4.10	5.00	25.30	40.95	88.52	164.25	152.35	119.96	159.71	89.04	103.74
61	25.54	6.34	6.82	1.73	0.63	4.11	34.34	48.20	161.47	112.20	91.46	95.20	73.28	85.37
137	71.58	17.49	26.43	17.66	7.90	18.69	39.13	71.37	175.58	159.65	113.40	140.40	85.80	114.48
336	36.05	12.62	15.53	1.77	0.96	6.47	31.51	43.22	113.53	92.45	99.88	123.50	159.92	96.08
1132	68.25	3.20	19.20	2.17	13.69	25.30	59.37	66.00	162.91	132.10	98.43	59.31	74.15	125.51
1340	56.58	13.06	21.04	12.24	18.09	22.73	38.81	47.63	237.27	204.96	176.84	346.51	167.31	134.73
1540	73.69	27.76	32.13	6.96	3.91	25.71	17.63	17.57	144.35	114.80	152.76	139.56	103.36	126.51
1613	39.26	5.18	16.04	13.55	14.70	19.28	18.30	39.25	155.21	119.51	107.74	164.23	125.38	122.92
1615	60.45	39.81	17.82	15.05	16.36	20.41	45.49	50.57	127.69	100.20	125.61	125.54	76.09	97.17
1616	81.11	31.13	46.69	29.45	8.98	24.15	37.63	32.25	115.10	74.43	89.58	77.81	52.83	80.71
1619	82.83	16.06	24.32	19.69	12.41	28.99	42.95	49.95	147.16	205.75	165.69	208.77	203.81	172.31
1632	54.74	17.02	11.74	4.83	4.99	12.45	20.07	37.10	151.01	135.47	147.94	162.22	101.99	157.04

TABLE 18

siRNA	FSHD Composite (% Mock)						ACTA 1 (% Mock)					
	10 nM						10 nM					
	MB01	MB02	MB03	MB04	MB05	MB06	MB10	MB11	MB12	MB02	MB06	
11	43.10	31.76	22.99	5.61	15.02	16.09	19.78	2.66	13.06	51.87	76.24	
57	60.89	25.86	35.58	81.33	16.05	14.22	33.53	29.01	43.75	64.82	38.21	
58	47.60	9.78	17.90	0.72	8.74	4.10	22.29	5.00	25.30	40.95	88.52	
61	25.54	6.34	12.59	0.59	6.82	1.73	16.50	0.63	4.11	34.34	48.10	
137	71.58	17.49	25.94	0.37	26.43	17.66	26.87	7.90	18.69	39.13	71.37	
336	36.05	12.62	15.99	0.13	15.53	1.77	11.35	0.96	6.47	31.51	43.22	
1132	68.25	3.20	15.18	8.72	19.20	2.17	34.72	13.69	25.30	59.37	66.00	
1340	56.58	13.06	41.13	13.67	21.04	12.24	35.26	18.09	22.73	38.81	47.63	
1540	73.69	27.76	39.02	6.94	32.13	6.96	27.94	3.910	25.71	17.63	17.57	
1613	39.16	5.18	13.19	76.57	16.04	13.55	84.76	14.70	19.28	18.30	39.25	
1615	60.45	39.81	34.04	12.48	17.82	15.05	41.32	16.36	20.41	45.49	50.57	
1616	81.11	31.13	36.27	13.99	46.99	24.95	72.30	8.98	24.15	37.63	32.25	
1619	82.83	16.06	40.97	3.88	24.32	19.69	41.16	12.41	28.99	42.95	49.95	
1632	54.74	17.02	19.15	4.02	11.74	4.83	28.31	4.99	12.45	20.07	37.10	

Example 9. Top 14 DUX4 siRNAs Evaluated for Potency in Concentration Response in MB02, MB05 and MB06

[0418] The goal of the experiments in this example is to select 8 siRNAs with best Emax and potency for off-target analysis. Three FSHD primary myoblast cell lines (MB02, MB05, MB06) were used. Cells were plated at a density of 4,000 cells/well (MW96) and transfected in quadruplicates

with selected 14 DUX4 siRNAs. Transfection was performed 24 hours after plating. Myogenic differentiation was induced 2 days after plating (24 hours after transfection) with 15% KOSR (in DMEM/F-12) medium. Samples were harvested 3 or 4 day's after inducing differentiation, depending on the cell line. DUX4-downstream target gene expression was evaluated by RT-qPCR (normalized to a composite AHSA1 and RPL27 housekeeping gene expression value). Data represented as mean-/+SEM. N=4.

[0419] FIGS. 16A-C show concentration response of 14 selected DUX4 siRNA in three FSHD patient-derived primary myotubes—MB02, MB05, MB06, respectively. DUX4-target gene expression was reduced more than 75% by most of the top 14 DUX4 siRNAs in three FSHD patient-derived primary myoblast lines. It was also observed that differences on potency among siRNAs ranged between 60 to 100-fold depending on the cell lines. Tables 19-22 show potency of DUX4 siRNAs evaluated in three FSHD patient-derived primary myotubes based on FSHD composite.

TABLE 19

MB02		
siRNA	Max KD (%)*	IC50 (nM)
11	95.54	1.506
57	90.06	0.918
58	100.00	1.969
61	100.00	0.639
137	93.30	1.903
336	83.74	0.110
1132	100.00	2.830
1340	83.69	2.137
1540	66.47	0.047
1613	95.09	0.259
1615	76.01	0.166
1616	88.05	0.372
1619	87.10	0.306
1632	91.52	0.082

TABLE 20

MB05		
siRNA	Max KD (%)*	IC50 (nM)
11	83.78	0.055
57	86.86	0.870
58	89.08	0.375
61	95.24	0.127
137	86.13	0.673
336	94.35	0.127
1132	100.00	2.666
1340	79.53	0.309
1540	91.33	0.075
1613	96.23	0.118
1615	82.43	0.091
1616	81.99	0.130
1619	78.60	0.091
1632	87.59	0.027

TABLE 21

MB06		
siRNA	Max KD (%)*	IC50 (nM)
11	90.75	1.923
57	68.18	0.054
58	98.45	1.374
61	100.00	0.665
137	87.25	2.018
336	98.53	0.359
1132	100.00	4.482
1340	100.00	1.090
1540	92.71	0.145
1613	84.07	0.070
1615	80.01	0.457
1616	67.81	0.051

TABLE 21-continued

MB06		
siRNA	Max KD (%)*	IC50 (nM)
1619	71.83	0.299
1632	93.15	0.243

TABLE 22

All lines together		
siRNA	Av. Max KD (%)*	Av. IC50 (nM)
11	90.02	1.161
57	81.70	0.614
58	95.84	1.239
61	98.41	0.477
137	88.89	1.531
336	92.21	0.199
1132	100.00	3.326
1340	87.74	1.179
1540	83.50	0.089
1613	91.80	0.149
1615	79.48	0.238
1616	79.28	0.184
1619	79.18	0.232
1632	90.76	0.117

Example 11

[0420] Antibody-DUX4 siRNA conjugates (DUX4-AOCs) mediated reduction of FSHD composite (composite of DUX4-target biomarker genes) expression in cultured FSHD primary myotubes.

[0421] The in vitro concentration-response potency and maximum efficacy of 16 DUX4-AOCs (8 vpUq AOCs or 8 Non-VP AOCs) were assessed in FSHD1 patient-derived primary myotubes (MB06). The guide strand of the DUX4 siRNA of the AOCs was either with vinylphosphonate at the 5' of the strand (vpUq) or without vinylphosphonate at the 5' end of the strand (Non-VP).

[0422] The human IgG1 antibody against human TfR1 was expressed in CHO stable pools, created by transfecting the CHOK1SV GS-KO host cell line with a double gene vector. The antibody was captured from cell culture supernatant using protein A affinity chromatography. The resultant antibody was further purified using hydrophobic interaction chromatography (to reduce aggregates) and anion exchange chromatography (to reduce host cell DNA & endotoxin). The final antibody was buffer exchanged into either PBS or 50 mM sodium citrate buffer, pH 6.5 at a concentration of 20 mg/mL. The purity of the antibody was assessed by size exclusion chromatography.

[0423] The guide and fully complementary RNA passenger strands were assembled on solid phase using standard phosphoramidite chemistry and purified over HPLC. Purified single strands were duplexed to obtain double stranded siRNA. The guide strand was produced with a vinylphosphonate modified nucleotide structures at the 5' end. The passenger strand had a conjugation handle on the 5' end via a phosphorothioate-inverted abasic-phosphodiester linker.

[0424] Antibody oligonucleotide conjugates (AOCs) were generated using a random cysteine conjugation method. The interchain disulfide bonds of the antibody were partially reduced with TCEP prior to conjugation with a maleimide linker-siRNA. The reaction mixture was purified using

strong anion exchange chromatography to ensure a drug-antibody ratio (DAR) equal to 1 (i.e., one siRNA molecule per one antibody molecule). Collected AOC fractions were concentrated, buffer exchanged into PBS and sterile filtered using a 0.2 μm filter. The purity of AOCs was assessed using strong anion exchange chromatography, size exclusion chromatography, and SDS-PAGE.

[0425] FSHD primary myoblasts (MB06 (FSHD1)) were grown in recommended media. Prior to seeding, 96-well tissue culture plates (Costar) were coated with 50 μL of 1% Matrigel per well for at least 2 hours at 37° C., and washed 2 \times with PBS. After coating, myoblasts were seeded in quadruplicate at 4000 cells/well. 2 days after plating, myogenic differentiation was induced with 15% KOSR-containing differentiation medium. 24 hours after inducing differentiation, siDUX4-AOCs were added in the medium at a high concentration of 100 nM with 10-fold serial dilutions. Untreated cells were maintained as a relative control. After 3 days of incubation with DUX4-AOCs, myotubes were collected in Trizol and stored at -80° C. until processing. RNA isolation was performed using Direct-zol-96 RNA isolation kit (Zymo) according to the manufacturer's instructions. 100-500 ng of purified RNA was converted to cDNA using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) using SimpliAmp Thermal Cycler (Applied Biosystems). cDNA was analyzed by qPCR using TaqMan Fast Universal Master Mix II (Thermo Fisher) and TaqMan probes (Thermo Fisher) in duplicates, using QuantStudio 6 or 7 Flex Real-Time PCR instruments (Applied Biosystems). Data were analyzed by QuantStudio™ Real-Time PCR Software v1.3 (Applied Biosystems). DUX4-target gene expression levels were evaluated by calculating the FSHD Composite score, which integrated the expression levels of 4 DUX4-target genes (MBD3L2, ZSCAN4, LEUTX, and KHDC1L) normalized to two reference genes (AHSA1 and RPL27).

[0426] FIGS. 18A-B show the dose response curve of DUX4-AOCs mediated reduction of DUX4-target biomarker gene expressions in cultured FSHD primary myotubes. Most DUX4-AOCs with vinylphosphonate (FIG. 18A) and several DUX4-AOCs without vinylphosphonate (FIG. 18B) reduced the expression of the FSHD composite of 4 DUX4-target biomarker genes (MBD3L2, ZSCAN4, LEUTX, and KHDC1L) in FSHD1 patient-derived primary myotubes. Overall, DUX4-AOCs reduced the expression of DUX4-target biomarker gene expressions and the presence of vinylphosphonate on the DUX4 siRNA in the AOCs facilitated the reduction of the DUX4-target biomarker gene expressions.

Example 12. Malat1-siRNA AOC Mediated In Vivo Reduction of Nuclear Localized Inc-RNA Malat1 mRNA Levels in 3 Different Murine Skeletal Muscles

[0427] Wild type female CD-1 mice (approximately 6-8 weeks old) were dosed once by a single IV bolus injection in the tail vein at 5 mL/kg body weight, of either Malat1 or Scramble AOCs, in which the siRNA was conjugated to murine anti-Transferrin Receptor (mTfR1) antibody, at doses 0.3, 1, 3, 6 mg/kg body weight (siRNA amount). Muscle tissue samples were collected 2 weeks post treatment in tubes containing ceramic beads, flash frozen in liquid nitrogen, and then homogenized in 1 mL cold Trizol using a FastPrep-24 (MP Biomedicals). Homogenate super-

natants were used for RNA isolation using Direct-zol-96 RNA isolation kit (Zymo) according to the manufacturer's instructions. 100-500 ng of purified RNA was converted to cDNA using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) using SimpliAmp Thermal Cycler (Applied Biosystems). cDNA was analyzed by qPCR using TaqMan Fast Universal Master Mix II (Thermo Fisher) and TaqMan probes (Thermo Fisher) in duplicates, using QuantStudio 6 or 7 Flex Real-Time PCR instruments (Applied Biosystems). Data were analyzed by QuantStudio™ Real-Time PCR Software v1.3 (Applied Biosystems). The target gene expression was normalized to a reference gene Ppib. The percentage of target mRNA expression in treatment samples was determined relative to the control treatment using the $2^{-\Delta\Delta C_t}$ method. Data are represented as % of PBS control (mean \pm SEM; N=4 for siMalat1 and siScramble AOCs, N=5 for PBS groups).

[0428] FIG. 19 shows Malat1 siRNA-AOC-mediated in vivo reduction of nuclear localized Inc-RNA Malat1 levels in skeletal muscles in mice. A single administration of up to 6 mg/kg of Malat1 siRNA-AOC (siRNA dose) in mice reduced nuclear Malat1 expression up to 80% in skeletal muscle 2 weeks post-dose. The reduction of nuclear Malat1 mRNA expression levels indicate the in vivo ability of AOCs to target nuclear RNAs for degradation.

Example 13. Sustained AOC-Mediated in Vivo Reduction of Ssb mRNA Levels in Murine Skeletal Muscles with a Single Dose of 3 mg/kg siRNA AOC During an 8-Week Period

[0429] Wild type male C57BL/6 mice (approximately 12-16 weeks old) were dosed once by a single IV bolus injection in the tail vein at 5 mL/kg body weight of either without vinylphosphonate (Non-VP) or with vinylphosphonate (vpUq) Ssb siRNA conjugated to murine anti-TfR1 (mTfR1) antibody at 3 mg/kg body weight (siRNA amount) dose. Gastrocnemius muscles were collected at the following time-points after dosing: day 1, 7, 14, 28, 43 and 57. Muscles were placed in tubes containing ceramic beads, flash frozen in liquid nitrogen, and then homogenized in 1 mL cold Trizol using a FastPrep-24 (MP Biomedicals). Homogenate supernatants were used for RNA isolation using Direct-zol-96 RNA isolation kit (Zymo) according to the manufacturer's instructions. 100-5(0) ng of purified RNA was converted to cDNA using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) using SimpliAmp Thermal Cycler (Applied Biosystems). cDNA was analyzed by qPCR using TaqMan Fast Universal Master Mix II (Thermo Fisher) and TaqMan probes (Thermo Fisher) in duplicates, using QuantStudio 6 or 7 Flex Real-Time PCR instruments (Applied Biosystems). Data were analyzed by QuantStudio™ Real-Time PCR Software v1.3 (Applied Biosystems). Ssb gene expression was normalized to the reference gene Ppib. The percentage of target mRNA expression in treatment samples was determined relative to the control treatment (PBS) using the $2^{-\Delta\Delta C_t}$ method. Data are represented as % of PBS control (mean \pm SEM; N=4 for siSsb-AOCs, N=3-5 for PBS groups).

[0430] FIG. 20 shows Ssb siRNA-AOC-mediated in vivo reduction of Ssb mRNA levels in murine skeletal muscles with a single dose of 3 mg/kg siRNA during an 8-week period. The sustained AOC-mediated in vivo reduction of Ssb mRNA expression levels was achieved in a mouse skeletal muscle after a 3 mg/kg (siRNA dose) single admin-

istration of both without vinylphosphonate (non-VP) and with vinylphosphonate (vpUq) SSB siRNA-AOCs.

[0431] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in

the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

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FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 84		
agccgttctc tgggtggcga		19

-continued

SEQ ID NO: 85	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 85		
ccggaatgcc gatggcctg		19
SEQ ID NO: 86	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 86		
ctccggaatg ccgatggcc		19
SEQ ID NO: 87	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 87		
gctccggaat gccgatggc		19
SEQ ID NO: 88	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 88		
ccgagattcc cgccgggtgc		19
SEQ ID NO: 89	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 89		
gccgagattc ccgcccgtg		19
SEQ ID NO: 90	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 90		
gctttcgcgc gcctttctg		19
SEQ ID NO: 91	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 91		
ccgctttcgc cggccttct		19
SEQ ID NO: 92	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 92		
tccgctttcg ccggccttc		19
SEQ ID NO: 93	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 93		
gacggcggtc cgctttcgc		19
SEQ ID NO: 94	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	

-continued

SEQUENCE: 94	organism = synthetic construct	
gtgacggcgg tccgcttcc		19
SEQ ID NO: 95	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 95		
atccggtgac ggcgggtccg		19
SEQ ID NO: 96	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 96		
gatccgggtga cggcgggtcc		19
SEQ ID NO: 97	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 97		
ggatccgggtg acggcgggtc		19
SEQ ID NO: 98	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 98		
gactccggga ggcccgtct		19
SEQ ID NO: 99	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 99		
gcgaaggcga cccacgagg		19
SEQ ID NO: 100	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 100		
ggcgaaggcg acccacgag		19
SEQ ID NO: 101	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 101		
caggttggga gatcccctc		19
SEQ ID NO: 102	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 102		
taggcgaaat ccccgcgcg		19
SEQ ID NO: 103	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 103		
gtaggcgaaa tccccgcgc		19

-continued

SEQ ID NO: 104	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 104		
ggcgtaggcg aaatccccg		19
SEQ ID NO: 105	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 105		
gacgtgggtg gcgcaagca		19
SEQ ID NO: 106	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 106		
gaaactccgg gctcgccag		19
SEQ ID NO: 107	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 107		
cagaaactcc gggctcgcc		19
SEQ ID NO: 108	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 108		
ttctaggaga ggttgcgcc		19
SEQ ID NO: 109	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 109		
tttctaggag aggttgcg		19
SEQ ID NO: 110	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 110		
tccgtttcta ggagaggtt		19
SEQ ID NO: 111	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 111		
ccggtattct tcctcgctg		19
SEQ ID NO: 112	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 112		
cccggtattc tcctcgct		19
SEQ ID NO: 113	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	

-continued

SEQUENCE: 113	organism = synthetic construct	
gcccggtatt cttctcgc		19
SEQ ID NO: 114	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 114		
caccgagccc cgtcccaac		19
SEQ ID NO: 115	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 115		
ccgaaccacc cgaccccgt		19
SEQ ID NO: 116	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 116		
tgccccgaac caccgacc		19
SEQ ID NO: 117	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 117		
ctgccccgaa ccaccgcac		19
SEQ ID NO: 118	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 118		
gcgaaagaga ggccaccgc		19
SEQ ID NO: 119	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 119		
cgcgaaagag aggccaccg		19
SEQ ID NO: 120	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 120		
ccgcgaaaga gaggccacc		19
SEQ ID NO: 121	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 121		
ttccccgcga aagagaggc		19
SEQ ID NO: 122	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 122		
ctccgtagcc agccagggtg		19

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SEQ ID NO: 123	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 123		
agacacgccc ctccgtagc		19
SEQ ID NO: 124	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 124		
gagacacgcc cctccgtag		19
SEQ ID NO: 125	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 125		
agcgagctcc cttgcacgt		19
SEQ ID NO: 126	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 126		
cagcgagctc cttgcacg		19
SEQ ID NO: 127	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 127		
ccagcgagct cccttgca		19
SEQ ID NO: 128	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 128		
tagacagcgt cggaaggtg		19
SEQ ID NO: 129	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 129		
ctagacagcg tcggaaggt		19
SEQ ID NO: 130	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 130		
cctagacagc gtcggaagg		19
SEQ ID NO: 131	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 131		
gcctagacag cgtcggaag		19
SEQ ID NO: 132	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	

-continued

SEQUENCE: 132	organism = synthetic construct	
ttgcctagac agcgtcggg		19
SEQ ID NO: 133	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 133		
tttgctaga cagcgtcgg		19
SEQ ID NO: 134	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 134		
aggtttgcct agacagcgt		19
SEQ ID NO: 135	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 135		
gtaactctaa tccaggttt		19
SEQ ID NO: 136	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 136		
aaagcgatcc ttctcaaag		19
SEQ ID NO: 137	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 137		
ggagatcccc tctgccggc		19
SEQ ID NO: 138	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 138		
cgcaagcacc ccttgccc		19
SEQ ID NO: 139	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 139		
ggcgcaagca ccccttggc		19
SEQ ID NO: 140	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 140		
gcgccgggat gccttgc		19
SEQ ID NO: 141	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	

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modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 141
cgacaccctc ggacagcaa                                     19

SEQ ID NO: 142      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                  1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base     2
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     4
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     5
                    mod_base = OTHER

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modified_base      note = 2'-O-methylcytidine
                   6
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  10
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  11
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  12
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  13
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  14
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                  18
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                  19
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine

SEQUENCE: 142
acggcgacgg agactcgta                                     19

SEQ ID NO: 143      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methylcytidine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-fluorocytidine
                   mod_base = OTHER
modified_base      9
                   note = 2'-fluoroguanosine

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modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   19
SEQUENCE: 143
cggcgacgga gactcgtaa                               19

SEQ ID NO: 144      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

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-continued

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modified_base      13
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      14
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      16
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 144
ggcgacggag actcgttta                                     19

SEQ ID NO: 145      multype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     16
                    mod_base = OTHER

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modified_base	note = 2'-O-methyluridine 17 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate 18 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate 19 mod_base = OTHER	
SEQUENCE: 145	note = 2'-O-methyladenosine	
gcgacggaga ctcgtttga		19
SEQ ID NO: 146	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19 mol_type = other RNA organism = synthetic construct	
modified_base	1 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate 2 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate 3 mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine 4 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 5 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine 6 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine 7 mod_base = OTHER	
modified_base	note = 2'-fluoroadenosine 8 mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine 9 mod_base = OTHER	
modified_base	note = 2'-fluoroadenosine 10 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 11 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine 12 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 13 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine 14 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine 15 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine 16 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine 17 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate 18 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate 19 mod_base = OTHER	
SEQUENCE: 146	note = 2'-O-methyladenosine	

-continued

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cgacggagac tcgtttgga                                     19

SEQ ID NO: 147      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                  mol_type = other RNA
                  organism = synthetic construct

modified_base      1
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                  mod_base = OTHER
                  note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      4
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      5
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      6
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base      7
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base      8
                  mod_base = OTHER
                  note = 2'-fluoroadenosine
modified_base      9
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     10
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     11
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     12
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     13
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     14
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     15
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     16
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     17
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     18
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base     19
                  mod_base = OTHER
                  note = 2'-O-methyladenosine phosphorothioate
                  mod_base = OTHER
                  note = 2'-O-methyladenosine

SEQUENCE: 147
gacggagact cgtttgaa                                     19

SEQ ID NO: 148      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                  mol_type = other RNA
                  organism = synthetic construct

modified_base      1
                  mod_base = OTHER
                  note = 2'-O-methyladenosine phosphorothioate
modified_base      2

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   3
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   4
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   6
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   7
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
                   8
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   9
modified_base      mod_base = OTHER
                   note = 2'-fluorouridine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   19
SEQUENCE: 148
acggagactc gtttgaca                                     19

SEQ ID NO: 149      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```

-continued

```

modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     14
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     16
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 149
ggaccccgag ccaaagcga                               19

SEQ ID NO: 150
FEATURE
source
mol_type = other RNA
organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base     10
                   mod_base = OTHER

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-continued

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modified_base      note = 2'-fluoroguanosine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine phosphorothioate
                   19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 150
gaccccgagc caaagcgaa                               19

SEQ ID NO: 151      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methyladenosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylcytidine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      7
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base     10
                   note = 2'-fluorocytidine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base     13
                   note = 2'-O-methyladenosine
                   mod_base = OTHER

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-continued

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modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   19
SEQUENCE: 151
accccgagcc aaagcgaga                               19

SEQ ID NO: 152      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methyluridine

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-continued

```

modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
SEQUENCE: 152
cctgcgagcc tgctttgaa                                     19

SEQ ID NO: 153      multype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
SEQUENCE: 153
gcgagcctgc tttgagcga                                     19

```

-continued

```

SEQ ID NO: 154      moltype = RNA length = 19
FEATURE           Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base    1
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base    2
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base    3
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    4
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base    5
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base    6
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base    7
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base    8
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base    9
                  mod_base = OTHER
                  note = 2'-fluoroadenosine
modified_base    10
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    11
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base    12
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    13
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base    14
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base    15
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base    16
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    17
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base    18
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base    19
                  mod_base = OTHER
                  note = 2'-O-methyladenosine

SEQUENCE: 154
tcgccaccag agaacggca                               19

SEQ ID NO: 155      moltype = RNA length = 19
FEATURE           Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base    1
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base    2
                  mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyladenosine phosphorothioate
                   3
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   4
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   6
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   7
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                  10
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  11
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  13
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  14
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                  18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                  19
                   mod_base = OTHER
SEQUENCE: 155      note = 2'-O-methyladenosine
caggccatcg gcattccga
                   19

SEQ ID NO: 156      moltype = RNA length = 19
FEATURE           Location/Qualifiers
source           1..19
                 mol_type = other RNA
                 organism = synthetic construct
modified_base    1
                 mod_base = OTHER
modified_base    2
                 note = 2'-O-methylguanosine phosphorothioate
                 mod_base = OTHER
modified_base    3
                 note = 2'-O-methylguanosine phosphorothioate
                 mod_base = OTHER
modified_base    4
                 note = 2'-O-methylcytidine
                 mod_base = OTHER
modified_base    5
                 note = 2'-O-methylcytidine
                 mod_base = OTHER
modified_base    6
                 note = 2'-O-methyladenosine

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   7
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   8
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   19
SEQUENCE: 156
ggccatcggc attccgga                                     19

SEQ ID NO: 157      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorocytidine

```

-continued

```

modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 157
gccatcggca ttccggaga                                     19

SEQ ID NO: 158      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     13
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyladenosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 158
gcaccggcgg gaatctcga                                     19

SEQ ID NO: 159      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      17

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-continued

	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 159		
caccggcggg aatctcgga		19
SEQ ID NO: 160	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	5	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	6	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	7	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	8	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	9	
	mod_base = OTHER	
modified_base	note = 2'-fluorocytidine	
	10	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	11	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	12	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	16	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	17	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 160		
ccagaaggcc ggcgaaaga		19

-continued

```

SEQ ID NO: 161      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-O-methyladenosine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base     3
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     4
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     5
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     6
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     7
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     8
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     9
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base     10
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     11
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     12
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     13
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     14
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     15
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     16
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     17
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base     18
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base     19
                  mod_base = OTHER
                  note = 2'-O-methyladenosine

SEQUENCE: 161
agaaggccgg cgaaagcga                               19

SEQ ID NO: 162      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-O-methyladenosine phosphorothioate

```

-continued

```

modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 162
gaaggccggc gaaagcgga                                     19

SEQ ID NO: 163      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                  1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     2
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     5
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     6
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyladenosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   19

SEQUENCE: 163
gcgaaagcgg accgccgta                                     19

SEQ ID NO: 164      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methyladenosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      8
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base     10
                   note = 2'-fluoroadenosine
                   mod_base = OTHER

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
12
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
14
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
16
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
18
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
19
SEQUENCE: 164
gaaagcggac cgccgtcaa                               19

SEQ ID NO: 165      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

```

-continued

```

modified_base      14
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 165
cggaccgccg tcaccgga                                     19

SEQ ID NO: 166      multype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     17
                    mod_base = OTHER

```

-continued

modified_base	note = 2'-O-methyladenosine phosphorothioate 18 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate 19 mod_base = OTHER	
SEQUENCE: 166		
ggaccgccgt caccgata		19
SEQ ID NO: 167	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19 mol_type = other RNA organism = synthetic construct	
modified_base	1 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate 2 mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate 3 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 4 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 5 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine 6 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 7 mod_base = OTHER	
modified_base	note = 2'-fluorocytidine 8 mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine 9 mod_base = OTHER	
modified_base	note = 2'-fluorouridine 10 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 11 mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine 12 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 13 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine 14 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine 15 mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine 16 mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine 17 mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate 18 mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate 19 mod_base = OTHER	
SEQUENCE: 167		
gaccgccgtc accggatca		19
SEQ ID NO: 168	moltype = RNA length = 19	

-continued

FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	5	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	6	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	7	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	8	
	mod_base = OTHER	
modified_base	note = 2'-fluorocytidine	
	9	
	mod_base = OTHER	
modified_base	note = 2'-fluorocytidine	
	10	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	11	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	12	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	16	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	17	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 168		
agacgggcct cccggagta		19
SEQ ID NO: 169	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	3	

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   4
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   6
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   7
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   8
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   19
SEQUENCE: 169
cctcgtgggt cgccttcga                               19

SEQ ID NO: 170      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylguanosine

```

-continued

```

modified_base      7
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 170
ctcgtgggtc gccttcgca                                     19

SEQ ID NO: 171      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                  1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     10
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyluridine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   19
                   mod_base = OTHER
SEQUENCE: 171      note = 2'-O-methyladenosine
gaggggatct cccaacctca                               19

SEQ ID NO: 172      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                  mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                  2
                  mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                  3
                  mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  4
                  mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  5
                  mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  6
                  mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  7
                  mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  8
                  mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  9
                  mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  10
                  mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  11
                  mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  12
                  mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  13
                  mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  14

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
16
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
18
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
SEQUENCE: 172
cgcgcgggga tttcgcta                               19

SEQ ID NO: 173      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylcytidine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base      10
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      11
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      12
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      13
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      14
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      15
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      16
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      17
                   note = 2'-O-methyluridine phosphorothioate

```

-continued

modified_base 18
 mod_base = OTHER
 note = 2'-O-methyladenosine phosphorothioate

modified_base 19
 mod_base = OTHER
 note = 2'-O-methyladenosine

SEQUENCE: 173
 gcgcggggat ttcgcctaa 19

SEQ ID NO: 174 moltype = RNA length = 19
 FEATURE Location/Qualifiers

source 1..19
 mol_type = other RNA
 organism = synthetic construct

modified_base 1
 mod_base = OTHER
 note = 2'-O-methylcytidine phosphorothioate

modified_base 2
 mod_base = OTHER
 note = 2'-O-methylguanosine phosphorothioate

modified_base 3
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 4
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 5
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 6
 mod_base = OTHER
 note = 2'-O-methyladenosine

modified_base 7
 mod_base = OTHER
 note = 2'-fluorouridine

modified_base 8
 mod_base = OTHER
 note = 2'-fluorouridine

modified_base 9
 mod_base = OTHER
 note = 2'-fluorouridine

modified_base 10
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 11
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 12
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 13
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 14
 mod_base = OTHER
 note = 2'-O-methyluridine

modified_base 15
 mod_base = OTHER
 note = 2'-O-methyladenosine

modified_base 16
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 17
 mod_base = OTHER
 note = 2'-O-methylguanosine phosphorothioate

modified_base 18
 mod_base = OTHER
 note = 2'-O-methylcytidine phosphorothioate

modified_base 19
 mod_base = OTHER
 note = 2'-O-methyladenosine

SEQUENCE: 174
 cggggatttc gcctacgca 19

SEQ ID NO: 175 moltype = RNA length = 19
 FEATURE Location/Qualifiers

-continued

```

source          1..19
                mol_type = other RNA
                organism = synthetic construct
modified_base  1
                mod_base = OTHER
                note = 2'-O-methyluridine phosphorothioate
modified_base  2
                mod_base = OTHER
                note = 2'-O-methylguanosine phosphorothioate
modified_base  3
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  4
                mod_base = OTHER
                note = 2'-O-methyluridine
modified_base  5
                mod_base = OTHER
                note = 2'-O-methyluridine
modified_base  6
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base  7
                mod_base = OTHER
                note = 2'-fluorocytidine
modified_base  8
                mod_base = OTHER
                note = 2'-fluoroguanosine
modified_base  9
                mod_base = OTHER
                note = 2'-fluorocytidine
modified_base  10
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  11
                mod_base = OTHER
                note = 2'-O-methyladenosine
modified_base  12
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  13
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  14
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  15
                mod_base = OTHER
                note = 2'-O-methyladenosine
modified_base  16
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  17
                mod_base = OTHER
                note = 2'-O-methylguanosine phosphorothioate
modified_base  18
                mod_base = OTHER
                note = 2'-O-methyluridine phosphorothioate
modified_base  19
                mod_base = OTHER
                note = 2'-O-methyladenosine

SEQUENCE: 175
tgcttgcgcc acccacgta                                     19

SEQ ID NO: 176      multype = RNA length = 19
FEATURE
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base    1
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base    2
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base    3
                  mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methylguanosine
                   4
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   6
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   19
                   mod_base = OTHER
SEQUENCE: 176
ctggcgagcc cggagttta                                     19

SEQ ID NO: 177      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-O-methylguanosine
                   mod_base = OTHER

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   8
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   9
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   19
SEQUENCE: 177
ggcgagcccg gagtttcta                               19

SEQ ID NO: 178      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyluridine

```


-continued

```

modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 178
ggcgcaacct ctctagaa                                     19

SEQ ID NO: 179      multype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyluridine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine phosphorothioate
                   19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 179
gcgcaacctc tcctagaaa                                     19

SEQ ID NO: 180      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      18

```

-continued

	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 180		
aacctctcct agaaacgga		19
SEQ ID NO: 181	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	5	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	6	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	7	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	8	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	9	
	mod_base = OTHER	
modified_base	note = 2'-fluoroadenosine	
	10	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	11	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	12	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	16	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	17	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 181		
cagcgaggaa gaataccga		19
SEQ ID NO: 182	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	

-continued

```

mol_type = other RNA
organism = synthetic construct
modified_base 1
mod_base = OTHER
note = 2'-O-methyladenosine phosphorothioate
modified_base 2
mod_base = OTHER
note = 2'-O-methylguanosine phosphorothioate
modified_base 3
mod_base = OTHER
note = 2'-O-methylcytidine
modified_base 4
mod_base = OTHER
note = 2'-O-methylguanosine
modified_base 5
mod_base = OTHER
note = 2'-O-methyladenosine
modified_base 6
mod_base = OTHER
note = 2'-O-methylguanosine
modified_base 7
mod_base = OTHER
note = 2'-fluoroguanosine
modified_base 8
mod_base = OTHER
note = 2'-fluoroadenosine
modified_base 9
mod_base = OTHER
note = 2'-fluoroadenosine
modified_base 10
mod_base = OTHER
note = 2'-O-methylguanosine
modified_base 11
mod_base = OTHER
note = 2'-O-methyladenosine
modified_base 12
mod_base = OTHER
note = 2'-O-methyladenosine
modified_base 13
mod_base = OTHER
note = 2'-O-methyluridine
modified_base 14
mod_base = OTHER
note = 2'-O-methyladenosine
modified_base 15
mod_base = OTHER
note = 2'-O-methylcytidine
modified_base 16
mod_base = OTHER
note = 2'-O-methylcytidine
modified_base 17
mod_base = OTHER
note = 2'-O-methylguanosine phosphorothioate
modified_base 18
mod_base = OTHER
note = 2'-O-methylguanosine phosphorothioate
modified_base 19
mod_base = OTHER
note = 2'-O-methyladenosine
SEQUENCE: 182
agcgaggaag aataccgga 19

SEQ ID NO: 183 moltype = RNA length = 19
FEATURE Location/Qualifiers
source 1..19
mol_type = other RNA
organism = synthetic construct
modified_base 1
mod_base = OTHER
note = 2'-O-methylguanosine phosphorothioate
modified_base 2
mod_base = OTHER
note = 2'-O-methylcytidine phosphorothioate
modified_base 3
mod_base = OTHER
note = 2'-O-methylguanosine

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-continued

```

modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 183
gcgaggaaga ataccggga                                     19

SEQ ID NO: 184      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                  1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      7
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-fluoroadenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   19
                   mod_base = OTHER
SEQUENCE: 184
gttgggacgg ggtcgggta                                     19

SEQ ID NO: 185      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methyladenosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylcytidine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-fluorouridine
                   mod_base = OTHER
modified_base      9
                   note = 2'-fluorocytidine
                   mod_base = OTHER
modified_base     10
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylguanosine
                   mod_base = OTHER

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   19
SEQUENCE: 185
acggggtcgg gtggttcga                               19

SEQ ID NO: 186      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methylguanosine

```

-continued

```

modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 186
ggtcgggtgg ttcggggca                               19

SEQ ID NO: 187   moltype = RNA length = 19
FEATURE         Location/Qualifiers
source          1..19
                mol_type = other RNA
                organism = synthetic construct
modified_base   1
                mod_base = OTHER
                note = 2'-O-methylguanosine phosphorothioate
modified_base   2
                mod_base = OTHER
                note = 2'-O-methyluridine phosphorothioate
modified_base   3
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base   4
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   5
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   6
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   7
                mod_base = OTHER
                note = 2'-fluorouridine
modified_base   8
                mod_base = OTHER
                note = 2'-fluoroguanosine
modified_base   9
                mod_base = OTHER
                note = 2'-fluoroguanosine
modified_base   10
                mod_base = OTHER
                note = 2'-O-methyluridine
modified_base   11
                mod_base = OTHER
                note = 2'-O-methyluridine
modified_base   12
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base   13
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   14
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   15
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   16
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base   17
                mod_base = OTHER
                note = 2'-O-methylcytidine phosphorothioate
modified_base   18
                mod_base = OTHER

```


-continued

modified_base	note = 2'-O-methyladenosine phosphorothioate 19 mod_base = OTHER note = 2'-O-methyladenosine	
SEQUENCE: 187		
gtcgggtggt tcggggcaa		19
SEQ ID NO: 188	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19 mol_type = other RNA organism = synthetic construct	
modified_base	1 mod_base = OTHER note = 2'-O-methylguanosine phosphorothioate	
modified_base	2 mod_base = OTHER note = 2'-O-methylcytidine phosphorothioate	
modified_base	3 mod_base = OTHER note = 2'-O-methylguanosine	
modified_base	4 mod_base = OTHER note = 2'-O-methylguanosine	
modified_base	5 mod_base = OTHER note = 2'-O-methyluridine	
modified_base	6 mod_base = OTHER note = 2'-O-methylguanosine	
modified_base	7 mod_base = OTHER note = 2'-fluoroguanosine	
modified_base	8 mod_base = OTHER note = 2'-fluorocytidine	
modified_base	9 mod_base = OTHER note = 2'-fluorocytidine	
modified_base	10 mod_base = OTHER note = 2'-O-methyluridine	
modified_base	11 mod_base = OTHER note = 2'-O-methylcytidine	
modified_base	12 mod_base = OTHER note = 2'-O-methyluridine	
modified_base	13 mod_base = OTHER note = 2'-O-methylcytidine	
modified_base	14 mod_base = OTHER note = 2'-O-methyluridine	
modified_base	15 mod_base = OTHER note = 2'-O-methyluridine	
modified_base	16 mod_base = OTHER note = 2'-O-methyluridine	
modified_base	17 mod_base = OTHER note = 2'-O-methylcytidine phosphorothioate	
modified_base	18 mod_base = OTHER note = 2'-O-methylguanosine phosphorothioate	
modified_base	19 mod_base = OTHER note = 2'-O-methyladenosine	
SEQUENCE: 188		
gcggtggcct ctctttcga		19
SEQ ID NO: 189	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19 mol_type = other RNA	

-continued

```

modified_base      organism = synthetic construct
                   1
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   2
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   3
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   4
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   6
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   19
                   mod_base = OTHER
SEQUENCE: 189      note = 2'-O-methyladenosine
eggtggcctc tctttcgca
                   19

SEQ ID NO: 190      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   2
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   3
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   4

```

-continued

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modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   6
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   7
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   8
modified_base      mod_base = OTHER
                   note = 2'-fluorouridine
                   9
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   14
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   16
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   19
SEQUENCE: 190
ggtggcctct ctttcgca                                     19

SEQ ID NO: 191      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluorocytidine

```

-continued

```

modified_base      8
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 191
gcctctcttt cgcggggaa                                     19

SEQ ID NO: 192      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                  1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     11
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methylguanosine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine phosphorothioate
                   19
                   mod_base = OTHER
SEQUENCE: 192
cacctggctg gctacggaa                                     19

SEQ ID NO: 193      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-O-methylcytidine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      7
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base     10
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     13
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     14
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     15
                   note = 2'-O-methylguanosine
                   mod_base = OTHER

```

-continued

	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	16	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	17	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	
modified_base	18	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 193		
gctacggagg ggcgtgtca		19
SEQ ID NO: 194	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	2	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	
modified_base	3	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
modified_base	4	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	5	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	6	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	7	
	mod_base = OTHER	
	note = 2'-fluoroadenosine	
modified_base	8	
	mod_base = OTHER	
	note = 2'-fluoroguanosine	
modified_base	9	
	mod_base = OTHER	
	note = 2'-fluoroguanosine	
modified_base	10	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	11	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	12	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	13	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	14	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	15	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	16	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	17	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	18	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	

-continued

```

modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 194
ctacggaggg gcgtgtcta                                     19

SEQ ID NO: 195      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct

modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     14
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     16
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 195
acgtgcaagg gagctcgca                                     19

SEQ ID NO: 196      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct

```

-continued

```

modified_base      1
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      6
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     14
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     16
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyladenosine

SEQUENCE: 196
cgtgcaaggg agctcgcta                                     19

SEQ ID NO: 197      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                  1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     2
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     4
                    mod_base = OTHER

```


-continued

```

modified_base      note = 2'-O-methylcytidine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   6
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  10
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  11
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  13
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  14
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  16
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  17
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                  18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                  19
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
SEQUENCE: 197
gtgcaaggga gctcgctga                                     19

SEQ ID NO: 198      moltype = RNA length = 19
FEATURE            Location/Qualifiers
source            1..19
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                  mod_base = OTHER
modified_base      2
                  note = 2'-O-methylcytidine phosphorothioate
                  mod_base = OTHER
modified_base      3
                  note = 2'-O-methyladenosine phosphorothioate
                  mod_base = OTHER
modified_base      4
                  note = 2'-O-methylcytidine
                  mod_base = OTHER
modified_base      5
                  note = 2'-O-methylcytidine
                  mod_base = OTHER
modified_base      6
                  note = 2'-O-methyluridine
                  mod_base = OTHER
modified_base      7
                  note = 2'-O-methyluridine
                  mod_base = OTHER
modified_base      8
                  note = 2'-fluorocytidine

```

-continued

	mod_base = OTHER	
	note = 2'-fluorocytidine	
modified_base	9	
	mod_base = OTHER	
	note = 2'-fluoroguanosine	
modified_base	10	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
modified_base	11	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	12	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	13	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	14	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	15	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	16	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	17	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	18	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	
modified_base	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 198		
caccttccga cgctgtcta		19
SEQ ID NO: 199	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
	note = 2'-O-methyladenosine phosphorothioate	
modified_base	2	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	3	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	4	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	5	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	6	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	7	
	mod_base = OTHER	
	note = 2'-fluorocytidine	
modified_base	8	
	mod_base = OTHER	
	note = 2'-fluoroguanosine	
modified_base	9	
	mod_base = OTHER	
	note = 2'-fluoroadenosine	
modified_base	10	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	11	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	

-continued

```

modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      14
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 199
accttcgac gctgtctaa                                     19

SEQ ID NO: 200      multype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     14
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     15
                   mod_base = OTHER

```

-continued

modified_base	note = 2'-O-methylcytidine 16 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 17 mod_base = OTHER
modified_base	note = 2'-O-methyladenosine phosphorothioate 18 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine phosphorothioate 19 mod_base = OTHER
SEQUENCE: 200	
ccttcgacg ctgtctaga	19
SEQ ID NO: 201	moltype = RNA length = 19
FEATURE	Location/Qualifiers
source	1..19 mol_type = other RNA organism = synthetic construct
modified_base	1 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine phosphorothioate 2 mod_base = OTHER
modified_base	note = 2'-O-methyluridine phosphorothioate 3 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 4 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 5 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 6 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 7 mod_base = OTHER
modified_base	note = 2'-fluoroadenosine 8 mod_base = OTHER
modified_base	note = 2'-fluorocytidine 9 mod_base = OTHER
modified_base	note = 2'-fluoroguanosine 10 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 11 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 12 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 13 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 14 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 15 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 16 mod_base = OTHER
modified_base	note = 2'-O-methyladenosine 17 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine phosphorothioate 18 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine phosphorothioate 19

-continued

	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 201		
cttccgacgc tgtctagga		19
SEQ ID NO: 202	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	
modified_base	2	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	3	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	4	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	5	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
modified_base	6	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	7	
	mod_base = OTHER	
	note = 2'-fluoroguanosine	
modified_base	8	
	mod_base = OTHER	
	note = 2'-fluorocytidine	
modified_base	9	
	mod_base = OTHER	
	note = 2'-fluorouridine	
modified_base	10	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	11	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	12	
	mod_base = OTHER	
	note = 2'-O-methylcytidine	
modified_base	13	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
modified_base	14	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
modified_base	15	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	16	
	mod_base = OTHER	
	note = 2'-O-methylguanosine	
modified_base	17	
	mod_base = OTHER	
	note = 2'-O-methylcytidine phosphorothioate	
modified_base	18	
	mod_base = OTHER	
	note = 2'-O-methyladenosine phosphorothioate	
modified_base	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 202		
tccgacgctg tctaggcaa		19
SEQ ID NO: 203	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	

-continued

	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	5	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	6	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	7	
	mod_base = OTHER	
modified_base	note = 2'-fluorocytidine	
	8	
	mod_base = OTHER	
modified_base	note = 2'-fluorouridine	
	9	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	10	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	11	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	12	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	16	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	17	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 203		
ccgacgctgt ctaggcaaa		19
SEQ ID NO: 204	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	

-continued

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modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     14
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     16
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 204
acgctgtcta ggcaaacca                                     19

SEQ ID NO: 205      moltype = RNA length = 19
FEATURE
source             Location/Qualifiers
                   1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      8
                   mod_base = OTHER

```

-continued

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modified_base      note = 2'-fluoroguanosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine phosphorothioate
                   19
                   mod_base = OTHER
SEQUENCE: 205      note = 2'-O-methyladenosine
aaacctggat tagagttaa
                   19

SEQ ID NO: 206      multype = RNA length = 19
FEATURE           Location/Qualifiers
source           1..19
                 mol_type = other RNA
                 organism = synthetic construct
modified_base    1
                 mod_base = OTHER
modified_base    2
                 note = 2'-O-methylcytidine phosphorothioate
                 mod_base = OTHER
modified_base    3
                 note = 2'-O-methyluridine phosphorothioate
                 mod_base = OTHER
modified_base    4
                 note = 2'-O-methyluridine
                 mod_base = OTHER
modified_base    5
                 note = 2'-O-methyluridine
                 mod_base = OTHER
modified_base    6
                 note = 2'-O-methylguanosine
                 mod_base = OTHER
modified_base    7
                 note = 2'-O-methyladenosine
                 mod_base = OTHER
modified_base    8
                 note = 2'-fluoroguanosine
                 mod_base = OTHER
modified_base    9
                 note = 2'-fluoroadenosine
                 mod_base = OTHER
modified_base   10
                 note = 2'-fluoroadenosine
                 mod_base = OTHER
modified_base   11
                 note = 2'-O-methylguanosine
                 mod_base = OTHER
modified_base   12
                 note = 2'-O-methylguanosine
                 mod_base = OTHER

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-continued

	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	16	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	17	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate	
	19	
	mod_base = OTHER	
	note = 2'-O-methyladenosine	
SEQUENCE: 206		
cttgagaag gatcgctta		19
SEQ ID NO: 207	moltype = RNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	5	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	6	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	7	
	mod_base = OTHER	
modified_base	note = 2'-fluoroadenosine	
	8	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	9	
	mod_base = OTHER	
modified_base	note = 2'-fluoroadenosine	
	10	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	11	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	12	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	

-continued

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modified_base      16
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

SEQUENCE: 207
gccggcagag gggatctca                                     19

SEQ ID NO: 208      multype = RNA length = 19
FEATURE            Location/Qualifiers
source             1..19
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     14
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     16
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     19
                   mod_base = OTHER

```

-continued

SEQUENCE: 208
ggccaagggt gcttgcga 19
note = 2'-O-methyladenosine

SEQ ID NO: 209
FEATURE
source
moltype = RNA length = 19
Location/Qualifiers
1..19
organism = synthetic construct
mol_type = other RNA

modified_base 1
mod_base = OTHER
note = 2'-O-methylguanosine phosphorothioate

modified_base 2
mod_base = OTHER
note = 2'-O-methylcytidine phosphorothioate

modified_base 3
mod_base = OTHER
note = 2'-O-methylcytidine

modified_base 4
mod_base = OTHER
note = 2'-O-methyladenosine

modified_base 5
mod_base = OTHER
note = 2'-O-methyladenosine

modified_base 6
mod_base = OTHER
note = 2'-O-methylguanosine

modified_base 7
mod_base = OTHER
note = 2'-fluoroguanosine

modified_base 8
mod_base = OTHER
note = 2'-fluoroguanosine

modified_base 9
mod_base = OTHER
note = 2'-fluoroguanosine

modified_base 10
mod_base = OTHER
note = 2'-O-methyluridine

modified_base 11
mod_base = OTHER
note = 2'-O-methylguanosine

modified_base 12
mod_base = OTHER
note = 2'-O-methylcytidine

modified_base 13
mod_base = OTHER
note = 2'-O-methyluridine

modified_base 14
mod_base = OTHER
note = 2'-O-methyluridine

modified_base 15
mod_base = OTHER
note = 2'-O-methylguanosine

modified_base 16
mod_base = OTHER
note = 2'-O-methylcytidine

modified_base 17
mod_base = OTHER
note = 2'-O-methylguanosine phosphorothioate

modified_base 18
mod_base = OTHER
note = 2'-O-methylcytidine phosphorothioate

modified_base 19
mod_base = OTHER
note = 2'-O-methyladenosine

SEQUENCE: 209
gccaaggggt gcttgcga 19

SEQ ID NO: 210
FEATURE
source
moltype = RNA length = 19
Location/Qualifiers
1..19
organism = synthetic construct
mol_type = other RNA

modified_base 1
mod_base = OTHER

-continued

modified_base	note = 2'-O-methyladenosine phosphorothioate 2 mod_base = OTHER
modified_base	note = 2'-O-methyluridine phosphorothioate 3 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 4 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 5 mod_base = OTHER
modified_base	note = 2'-O-methyladenosine 6 mod_base = OTHER
modified_base	note = 2'-O-methyladenosine 7 mod_base = OTHER
modified_base	note = 2'-fluoroguanosine 8 mod_base = OTHER
modified_base	note = 2'-fluoroguanosine 9 mod_base = OTHER
modified_base	note = 2'-fluorocytidine 10 mod_base = OTHER
modified_base	note = 2'-O-methyladenosine 11 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 12 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 13 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 14 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 15 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 16 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 17 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine phosphorothioate 18 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine phosphorothioate 19 mod_base = OTHER
SEQUENCE: 210	note = 2'-O-methyladenosine
atgcaaggca tccccggcga	
	19
SEQ ID NO: 211	moltype = RNA length = 21
FEATURE	Location/Qualifiers
source	1..21 mol_type = other RNA organism = synthetic construct
modified_base	1 mod_base = OTHER
modified_base	note = 2'-fluorouridine phosphorothioate 2 mod_base = OTHER
modified_base	note = 2'-fluorouridine phosphorothioate 3 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 4 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 5 mod_base = OTHER

-continued

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modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   6
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   7
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 211
ttgctgtccg aggggtgcgt t                               21

SEQ ID NO: 212      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-fluoroadenosine phosphorothioate
modified_base     3
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     4
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     5
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     6
                  mod_base = OTHER
                  note = 2'-fluoroguanosine

```

-continued

```

modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     21
                    mod_base = OTHER
                    note = 2'-O-methyluridine
SEQUENCE: 212
tacgagtctc cgtcgcccgtt t
                                           21

SEQ ID NO: 213      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                    1..21
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      8
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyluridine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 213
taacgagtct ccgtcgccgt t                                     21

SEQ ID NO: 214      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluoroadenosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     10
                   note = 2'-O-methyluridine
                   mod_base = OTHER

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
11
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
12
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
14
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
15
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
16
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 214
taaacgagtc tccgtcgct t                                     21

SEQ ID NO: 215      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```


-continued

```

modified_base      12
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      13
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      16
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base      20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 215
tcaaacgagt ctccgctcgt t                                     21

SEQ ID NO: 216      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluorocytidine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     13
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyluridine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 216
tccaacgag tctccgtgt t                                     21

SEQ ID NO: 217      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     10
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     13
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base     14
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     15
                   note = 2'-fluorouridine

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
16
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 217
ttccaaacga gtctccgtct t                               21

SEQ ID NO: 218      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluorocytidine

```

-continued

```

modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      21
                    mod_base = OTHER
                    note = 2'-O-methyluridine
SEQUENCE: 218
tgtccaaacg agtctccggt t                               21

SEQ ID NO: 219      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluorocytidine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     18
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methylcytidine
19
mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
20
mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
21
mod_base = OTHER
note = 2'-O-methyluridine
SEQUENCE: 219
tcgctttggc tcggggtcct t                                     21

SEQ ID NO: 220      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base      2
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base      3
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      4
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      5
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      6
                  mod_base = OTHER
                  note = 2'-fluorouridine
modified_base      7
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base      8
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base      9
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      10
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      11
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      12
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base      13
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      14
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base      15
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      16
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base      17
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      18
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base      19
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base      20

```

-continued

```

                mod_base = OTHER
                note = 2'-O-methyluridine phosphorothioate
modified_base 21
                mod_base = OTHER
                note = 2'-O-methyluridine
SEQUENCE: 220
ttcgctttgg ctcggggtct t                               21

SEQ ID NO: 221      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-fluorocytidine phosphorothioate
modified_base     3
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     4
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     5
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     6
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     7
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     8
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     9
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base    10
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    11
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    12
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base    13
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base    14
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base    15
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    16
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base    17
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    18
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    19
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base    20
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base    21
                  mod_base = OTHER
                  note = 2'-O-methyluridine

```

-continued

```

SEQUENCE: 221
tctcgctttg gctcggggtt t                               21

SEQ ID NO: 222      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base     3
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     4
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     5
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     6
                  mod_base = OTHER
                  note = 2'-fluoroadenosine
modified_base     7
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     8
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     9
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base    10
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    11
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    12
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base    13
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base    14
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base    15
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    16
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base    17
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base    18
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base    19
                  mod_base = OTHER
                  note = 2'-O-methylguanosine phosphorothioate
modified_base    20
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base    21
                  mod_base = OTHER
                  note = 2'-O-methyluridine

SEQUENCE: 222
ttcaaagcag gctcgcaggt t                               21

SEQ ID NO: 223      moltype = RNA length = 21
FEATURE            Location/Qualifiers

```

-continued

```

source          1..21
                mol_type = other RNA
                organism = synthetic construct
modified_base  1
                mod_base = OTHER
                note = 2'-fluorouridine phosphorothioate
modified_base  2
                mod_base = OTHER
                note = 2'-fluorocytidine phosphorothioate
modified_base  3
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base  4
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  5
                mod_base = OTHER
                note = 2'-O-methyluridine
modified_base  6
                mod_base = OTHER
                note = 2'-fluorocytidine
modified_base  7
                mod_base = OTHER
                note = 2'-O-methyladenosine
modified_base  8
                mod_base = OTHER
                note = 2'-O-methyladenosine
modified_base  9
                mod_base = OTHER
                note = 2'-O-methyladenosine
modified_base  10
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base  11
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  12
                mod_base = OTHER
                note = 2'-O-methyladenosine
modified_base  13
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base  14
                mod_base = OTHER
                note = 2'-fluoroguanosine
modified_base  15
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  16
                mod_base = OTHER
                note = 2'-fluorouridine
modified_base  17
                mod_base = OTHER
                note = 2'-O-methylcytidine
modified_base  18
                mod_base = OTHER
                note = 2'-O-methylguanosine
modified_base  19
                mod_base = OTHER
                note = 2'-O-methylcytidine phosphorothioate
modified_base  20
                mod_base = OTHER
                note = 2'-O-methyluridine phosphorothioate
modified_base  21
                mod_base = OTHER
                note = 2'-O-methyluridine

SEQUENCE: 223
tcgctcaag caggctcgct t

SEQ ID NO: 224      moltype = RNA length = 21
FEATURE
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base    1
                  mod_base = OTHER

```

21

-continued

modified_base	note = 2'-fluorouridine phosphorothioate 2 mod_base = OTHER
modified_base	note = 2'-fluoroguanosine phosphorothioate 3 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 4 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 5 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 6 mod_base = OTHER
modified_base	note = 2'-fluorouridine 7 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 8 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 9 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 10 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 11 mod_base = OTHER
modified_base	note = 2'-O-methyluridine 12 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 13 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 14 mod_base = OTHER
modified_base	note = 2'-fluorouridine 15 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 16 mod_base = OTHER
modified_base	note = 2'-fluoroguanosine 17 mod_base = OTHER
modified_base	note = 2'-O-methylcytidine 18 mod_base = OTHER
modified_base	note = 2'-O-methylguanosine 19 mod_base = OTHER
modified_base	note = 2'-O-methyladenosine phosphorothioate 20 mod_base = OTHER
modified_base	note = 2'-O-methyluridine phosphorothioate 21 mod_base = OTHER
modified_base	note = 2'-O-methyluridine

SEQUENCE: 224
tgccgttctc tgggtggcgat t 21

SEQ ID NO: 225	moltype = RNA length = 21
FEATURE	Location/Qualifiers
source	1..21
	mol_type = other RNA
	organism = synthetic construct
modified_base	1 mod_base = OTHER
modified_base	note = 2'-fluorouridine phosphorothioate 2 mod_base = OTHER
modified_base	note = 2'-fluorocytidine phosphorothioate 3

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   4
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   6
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
                   7
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   21
SEQUENCE: 225
tcggaatgcc gatggcctgt t                               21

SEQ ID NO: 226      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```

-continued

```

modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 226
ttccggaatg ccgatggcct t                                     21

SEQ ID NO: 227      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                  1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluorocytidine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      6
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-fluoroguanosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  10
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  11
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  14
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  15
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  16
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                  17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  19
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                  20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                  21
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine

SEQUENCE: 227
tctccggaat gccgatggct t                                     21

SEQ ID NO: 228      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluorocytidine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyluridine

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   21
SEQUENCE: 228
tcgagattcc cgccggtgct t
SEQ ID NO: 229      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methyluridine

```

-continued

```

modified_base      10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      13
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      16
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base      20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 229
tccgagattc cgcggtgt t                                     21

SEQ ID NO: 230      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluorocytidine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     11
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methylguanosine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 230
tccttcgccg gccttctggt t                                     21

SEQ ID NO: 231      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluorocytidine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluorouridine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     10
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     13
                   note = 2'-O-methylguanosine
                   mod_base = OTHER

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluorouridine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 231
tcgctttcgc cggccttctt t                               21

SEQ ID NO: 232      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluoroguanosine

```


-continued

```

modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 232
tccgctttcg cggccttct t                               21

SEQ ID NO: 233      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     16
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-fluorouridine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 233
tacggcggtc cgcttgcgt t                               21

SEQ ID NO: 234      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base      2
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base      3
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      4
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base      5
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      6
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base      7
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      8
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      9
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      10
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base      11
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base      12
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      13
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      14
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base      15
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base      16
                  mod_base = OTHER
                  note = 2'-fluorouridine
modified_base      17
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base      18

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 234
ttgacggcgg tccgctttct t                               21

SEQ ID NO: 235      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     10
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     13
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     14
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     15
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base     16
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     17
                   note = 2'-fluorouridine
                   mod_base = OTHER
modified_base     18
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     19
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     20
                   note = 2'-O-methylguanosine phosphorothioate

```

-continued

```

modified_base      20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 235
ttcggtgac ggcggtcggt t                                     21

SEQ ID NO: 236      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base     21
                   mod_base = OTHER

```

-continued

note = 2'-O-methyluridine
 SEQUENCE: 236
 tatccggtga cggcggctct t 21

SEQ ID NO: 237 moltype = RNA length = 21
 FEATURE Location/Qualifiers
 source 1..21
 mol_type = other RNA
 organism = synthetic construct

modified_base 1
 mod_base = OTHER
 note = 2'-fluorouridine phosphorothioate

modified_base 2
 mod_base = OTHER
 note = 2'-fluoroguanosine phosphorothioate

modified_base 3
 mod_base = OTHER
 note = 2'-O-methyladenosine

modified_base 4
 mod_base = OTHER
 note = 2'-O-methyluridine

modified_base 5
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 6
 mod_base = OTHER
 note = 2'-fluorocytidine

modified_base 7
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 8
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 9
 mod_base = OTHER
 note = 2'-O-methyluridine

modified_base 10
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 11
 mod_base = OTHER
 note = 2'-O-methyladenosine

modified_base 12
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 13
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 14
 mod_base = OTHER
 note = 2'-fluoroguanosine

modified_base 15
 mod_base = OTHER
 note = 2'-O-methylcytidine

modified_base 16
 mod_base = OTHER
 note = 2'-fluoroguanosine

modified_base 17
 mod_base = OTHER
 note = 2'-O-methylguanosine

modified_base 18
 mod_base = OTHER
 note = 2'-O-methyluridine

modified_base 19
 mod_base = OTHER
 note = 2'-O-methylcytidine phosphorothioate

modified_base 20
 mod_base = OTHER
 note = 2'-O-methyluridine phosphorothioate

modified_base 21
 mod_base = OTHER
 note = 2'-O-methyluridine

SEQUENCE: 237
 tgatccggtg acggcggctct t 21

SEQ ID NO: 238 moltype = RNA length = 21

-continued

FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	
	mod_base = OTHER	
modified_base	note = 2'-fluorouridine phosphorothioate	
	2	
	mod_base = OTHER	
modified_base	note = 2'-fluoroadenosine phosphorothioate	
	3	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	4	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	5	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	6	
	mod_base = OTHER	
modified_base	note = 2'-fluorocytidine	
	7	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	8	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	9	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	10	
	mod_base = OTHER	
modified_base	note = 2'-O-methyladenosine	
	11	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	12	
	mod_base = OTHER	
modified_base	note = 2'-O-methylguanosine	
	13	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	14	
	mod_base = OTHER	
modified_base	note = 2'-fluorocytidine	
	15	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	16	
	mod_base = OTHER	
modified_base	note = 2'-fluoroguanosine	
	17	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine	
	18	
	mod_base = OTHER	
modified_base	note = 2'-O-methylcytidine	
	19	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate	
	20	
	mod_base = OTHER	
modified_base	note = 2'-O-methyluridine phosphorothioate	
	21	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
SEQUENCE: 238		
tactccggga ggcccgtctt t		21
SEQ ID NO: 239	moltype = RNA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = other RNA	
	organism = synthetic construct	
modified_base	1	

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
                   2
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
                   3
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   4
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   6
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   7
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                  10
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                  11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                  12
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                  13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                  14
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
                  15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                  16
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                  17
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                  18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                  19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                  20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                  21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 239
tcgaaggcga cccacgaggt t                                     21

SEQ ID NO: 240      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate

```

-continued

```

modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     16
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base     20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base     21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 240
tgcaaggcg acccagagt t                                     21

SEQ ID NO: 241      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER

```


-continued

```

modified_base      note = 2'-O-methylguanosine
                    5
                    mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                    6
                    mod_base = OTHER
modified_base      note = 2'-fluorouridine
                    7
                    mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                    8
                    mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                    9
                    mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   10
                    mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   11
                    mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   12
                    mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   13
                    mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   14
                    mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   15
                    mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                    mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   17
                    mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   18
                    mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   19
                    mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   20
                    mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 241
taggttgga gatcccctct t                                     21

SEQ ID NO: 242      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
modified_base      note = 2'-fluorouridine phosphorothioate
                    2
                    mod_base = OTHER
modified_base      note = 2'-fluoroadenosine phosphorothioate
                    3
                    mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                    4
                    mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                    5
                    mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                    6

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   7
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   21
SEQUENCE: 242
taggcgaaat ccccgcgct t                               21

SEQ ID NO: 243      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine

```

-continued

```

modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base     21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 243
ttagcggaat tccccgcgct t                                     21

SEQ ID NO: 244      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methylcytidine
10
mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
11
mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
12
mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
13
mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
14
mod_base = OTHER
modified_base      note = 2'-fluorouridine
15
mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
16
mod_base = OTHER
modified_base      note = 2'-fluorocytidine
17
mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
18
mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
19
mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
20
mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
21
mod_base = OTHER
note = 2'-O-methyluridine

SEQUENCE: 244
tgcgtaggcg aaatccccgt t

SEQ ID NO: 245      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      4
                   note = 2'-O-methylcytidine
modified_base      5
                   note = 2'-O-methylguanosine
modified_base      6
                   note = 2'-O-methyluridine
modified_base      7
                   note = 2'-fluoroguanosine
modified_base      8
                   note = 2'-O-methylguanosine
modified_base      9
                   note = 2'-O-methylguanosine
modified_base     10
                   note = 2'-O-methyluridine
modified_base     11
                   note = 2'-O-methylguanosine

```

21

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
12
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
13
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
15
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
16
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 245
tacgtgggtg gcgcaagcat t                               21

SEQ ID NO: 246      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```

-continued

```

modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base      20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 246
taaactcegg gctcgccagt t                               21

SEQ ID NO: 247      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     14
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-fluorocytidine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 247
tagaaactcc gggctcgct t                                     21

SEQ ID NO: 248      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      16

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 248
ttctaggaga ggttgcgct t                               21

SEQ ID NO: 249      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```


-continued

```

modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 249
tttctaggag aggttgcgct t                                     21

SEQ ID NO: 250      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     19
                   mod_base = OTHER

```

-continued

modified_base note = 2'-O-methyluridine phosphorothioate
 20
 mod_base = OTHER
 modified_base note = 2'-O-methyluridine phosphorothioate
 21
 mod_base = OTHER
 note = 2'-O-methyluridine
 SEQUENCE: 250
 tccgtttcta ggagaggttt t 21

SEQ ID NO: 251 moltype = RNA length = 21
 FEATURE Location/Qualifiers
 source 1..21
 mol_type = other RNA
 organism = synthetic construct

modified_base 1
 mod_base = OTHER
 note = 2'-fluorouridine phosphorothioate
 modified_base 2
 mod_base = OTHER
 note = 2'-fluorocytidine phosphorothioate
 modified_base 3
 mod_base = OTHER
 note = 2'-O-methylguanosine
 modified_base 4
 mod_base = OTHER
 note = 2'-O-methylguanosine
 modified_base 5
 mod_base = OTHER
 note = 2'-O-methyluridine
 modified_base 6
 mod_base = OTHER
 note = 2'-fluoroadenosine
 modified_base 7
 mod_base = OTHER
 note = 2'-O-methyluridine
 modified_base 8
 mod_base = OTHER
 note = 2'-O-methyluridine
 modified_base 9
 mod_base = OTHER
 note = 2'-O-methylcytidine
 modified_base 10
 mod_base = OTHER
 note = 2'-O-methyluridine
 modified_base 11
 mod_base = OTHER
 note = 2'-O-methyluridine
 modified_base 12
 mod_base = OTHER
 note = 2'-O-methylcytidine
 modified_base 13
 mod_base = OTHER
 note = 2'-O-methylcytidine
 modified_base 14
 mod_base = OTHER
 note = 2'-fluorouridine
 modified_base 15
 mod_base = OTHER
 note = 2'-O-methylcytidine
 modified_base 16
 mod_base = OTHER
 note = 2'-fluoroguanosine
 modified_base 17
 mod_base = OTHER
 note = 2'-O-methylcytidine
 modified_base 18
 mod_base = OTHER
 note = 2'-O-methyluridine
 modified_base 19
 mod_base = OTHER
 note = 2'-O-methylguanosine phosphorothioate
 modified_base 20
 mod_base = OTHER
 note = 2'-O-methyluridine phosphorothioate
 modified_base 21

-continued

```

mod_base = OTHER
note = 2'-O-methyluridine
SEQUENCE: 251
tcggtattct tcctcgctgt t 21

SEQ ID NO: 252      moltype = RNA length = 21
FEATURE           Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-fluorocytidine phosphorothioate
modified_base     3
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     4
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     5
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     6
                  mod_base = OTHER
                  note = 2'-fluorouridine
modified_base     7
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     8
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     9
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     10
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     11
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     12
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     13
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     14
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     15
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     16
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     17
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     18
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     19
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base     20
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base     21
                  mod_base = OTHER
                  note = 2'-O-methyluridine
SEQUENCE: 252
tccggtattc ttctcgctt t 21

```

-continued

```

SEQ ID NO: 253      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                  mod_base = OTHER
                  note = 2'-fluorouridine phosphorothioate
modified_base     2
                  mod_base = OTHER
                  note = 2'-fluorocytidine phosphorothioate
modified_base     3
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     4
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     5
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     6
                  mod_base = OTHER
                  note = 2'-fluoroguanosine
modified_base     7
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     8
                  mod_base = OTHER
                  note = 2'-O-methyladenosine
modified_base     9
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     10
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     11
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     12
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     13
                  mod_base = OTHER
                  note = 2'-O-methyluridine
modified_base     14
                  mod_base = OTHER
                  note = 2'-fluorocytidine
modified_base     15
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     16
                  mod_base = OTHER
                  note = 2'-fluorouridine
modified_base     17
                  mod_base = OTHER
                  note = 2'-O-methylcytidine
modified_base     18
                  mod_base = OTHER
                  note = 2'-O-methylguanosine
modified_base     19
                  mod_base = OTHER
                  note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                  mod_base = OTHER
                  note = 2'-O-methyluridine phosphorothioate
modified_base     21
                  mod_base = OTHER
                  note = 2'-O-methyluridine

SEQUENCE: 253
tcceggatt ctctctcgct t

SEQ ID NO: 254      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct

```

-continued

```

modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 254
taccgaccc cgteccaact t

SEQ ID NO: 255      moltype = RNA length = 21
FEATURE
source             1..21
                    mol_type = other RNA
                    organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER

```

21

-continued

```

modified_base      note = 2'-fluorocytidine phosphorothioate
                   3
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   4
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   6
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   7
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   8
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine

SEQUENCE: 255
tcgaaccacc cgaccccggt t                                     21

SEQ ID NO: 256      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                  mod_base = OTHER
modified_base      2
                  note = 2'-fluorouridine phosphorothioate
                  mod_base = OTHER
modified_base      3
                  note = 2'-fluoroguanosine phosphorothioate
                  mod_base = OTHER
modified_base      4
                  note = 2'-O-methylcytidine

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   6
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   7
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
SEQUENCE: 256
tgccccgaac caccgcacct t                               21

SEQ ID NO: 257      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```

-continued

```

modified_base      6
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 257
ttgccccgaa ccaccgcgact t                                     21

SEQ ID NO: 258      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                    mol_type = other RNA
                    organism = synthetic construct
modified_base     1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base     2
                    mod_base = OTHER
                    note = 2'-fluorocytidine phosphorothioate
modified_base     3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     5
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     6
                    mod_base = OTHER
                    note = 2'-fluoroadenosine
modified_base     7
                    mod_base = OTHER

```


-continued

```

modified_base      note = 2'-O-methylguanosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 258
tcgaaagaga ggccaccgct t                                     21

SEQ ID NO: 259      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluoroguanosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methylguanosine
                   mod_base = OTHER

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
10
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
11
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
12
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
13
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
16
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
SEQUENCE: 259
tgcgaaagag aggccaccgt t                               21

SEQ ID NO: 260      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

```

-continued

```

modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 260
tcgcgaaaga gaggccacct t                               21

SEQ ID NO: 261      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     12
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyladenosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 261
ttccccgcga aagagaggct t      21

SEQ ID NO: 262      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 262
ttccgtagcc agccaggtgt t                               21

SEQ ID NO: 263      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source            1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylguanosine

```

-continued

```

modified_base      16
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base      20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 263
tgacacgccc ctccgtagct t                                     21

SEQ ID NO: 264      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluorocytidine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     17
                   mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methyluridine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 264
tagacacgcc cctccgtagt t                               21

SEQ ID NO: 265      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      19

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 265
tgcgagctcc cttgcacgtt t                               21

SEQ ID NO: 266      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluoroadenosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroadenosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     10
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     13
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     14
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base     15
                   note = 2'-fluorouridine
                   mod_base = OTHER
modified_base     16
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base     17
                   note = 2'-fluorocytidine
                   mod_base = OTHER
modified_base     18
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base     19
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     20
                   note = 2'-O-methylguanosine phosphorothioate
                   mod_base = OTHER
modified_base     21
                   note = 2'-O-methyluridine phosphorothioate

```


-continued

```

modified_base      21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 266
tagcgagctc ccttgacgt t                                     21

SEQ ID NO: 267      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct

modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     10
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     14
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base     15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base     16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base     17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     18
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     19
                   mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
modified_base     20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base     21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 267
tcagcgagct cccttgact t                                     21

```

-continued

```

SEQ ID NO: 268      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base     1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base     2
                   mod_base = OTHER
                   note = 2'-fluoroadenosine phosphorothioate
modified_base     3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     4
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base     5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     6
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base     7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base     8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base     9
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base    10
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base    11
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base    12
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base    13
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base    14
                   mod_base = OTHER
                   note = 2'-fluoroadenosine
modified_base    15
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base    16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base    17
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base    18
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base    19
                   mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
modified_base    20
                   mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
modified_base    21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 268
tagacagcgt cgaaggtgt t                                     21

```

```

SEQ ID NO: 269      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA

```

-continued

```

modified_base      organism = synthetic construct
                   1
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine phosphorothioate
                   2
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine phosphorothioate
                   3
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   4
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   6
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   7
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  10
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  11
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                  12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                  13
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  14
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                  15
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                  16
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                  17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                  19
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                  20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                  21
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine

SEQUENCE: 269
ttagacagcg tcggaaggtt t

SEQ ID NO: 270      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate

```

21

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
                   3
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   4
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   5
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   6
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
                   7
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluoroguanosine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 270
tctagacagc gtcggaaggt t                               21

SEQ ID NO: 271      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                   1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```

-continued

```

modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methylguanosine phosphorothioate
modified_base     20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 271
tcctagacag cgtcggaagt t                                     21

SEQ ID NO: 272      moltype = RNA length = 21
FEATURE
source             Location/Qualifiers
                  1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      5
                    mod_base = OTHER

```

-continued

```

modified_base      note = 2'-O-methylcytidine
                   6
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                   7
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   21

SEQUENCE: 272
ttgcctagac agcgtcggat t                               21

SEQ ID NO: 273      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluorocytidine

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   8
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   9
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   10
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   11
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   12
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
                   13
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   14
modified_base      mod_base = OTHER
                   note = 2'-fluorocytidine
                   15
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   16
modified_base      mod_base = OTHER
                   note = 2'-fluorouridine
                   17
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
                   18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
                   19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
                   20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
                   21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
                   21
SEQUENCE: 273
ttgcctaga cagcgtcgg t                               21

SEQ ID NO: 274      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine

```

-continued

```

modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base     15
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     16
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base     17
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base     19
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base     21
                    mod_base = OTHER
                    note = 2'-O-methyluridine

SEQUENCE: 274
tgggttgct agacagcgtt t                                     21

SEQ ID NO: 275      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base     1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base     2
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base     3
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base     5
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     6
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base     7
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     8
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     9
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base    10
                    mod_base = OTHER

```


-continued

```

modified_base      note = 2'-O-methyladenosine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 275
ttaaactctaa tccaggtttt t

SEQ ID NO: 276      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      2
                   note = 2'-fluorouridine phosphorothioate
                   mod_base = OTHER
modified_base      3
                   note = 2'-fluoroadenosine phosphorothioate
                   mod_base = OTHER
modified_base      4
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      5
                   note = 2'-O-methylguanosine
                   mod_base = OTHER
modified_base      6
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base      7
                   note = 2'-fluoroguanosine
                   mod_base = OTHER
modified_base      8
                   note = 2'-O-methyladenosine
                   mod_base = OTHER
modified_base      9
                   note = 2'-O-methyluridine
                   mod_base = OTHER
modified_base     10
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     11
                   note = 2'-O-methylcytidine
                   mod_base = OTHER
modified_base     12
                   note = 2'-O-methyluridine

```

-continued

```

modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
13
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
14
modified_base      mod_base = OTHER
                   note = 2'-fluorouridine
15
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine
16
modified_base      mod_base = OTHER
                   note = 2'-fluoroadenosine
17
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methyladenosine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine

SEQUENCE: 276
taagcgatcc ttctcaaagt t                               21

SEQ ID NO: 277      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct

modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methyluridine

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-continued

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modified_base      14
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      15
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      16
                    mod_base = OTHER
                    note = 2'-fluorocytidine
modified_base      17
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      18
                    mod_base = OTHER
                    note = 2'-O-methylguanosine
modified_base      19
                    mod_base = OTHER
                    note = 2'-O-methylcytidine phosphorothioate
modified_base      20
                    mod_base = OTHER
                    note = 2'-O-methyluridine phosphorothioate
modified_base      21
                    mod_base = OTHER
                    note = 2'-O-methyluridine
SEQUENCE: 277
tgagatcccc tctgcccgct t                                     21

SEQ ID NO: 278      multype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                  mol_type = other RNA
                  organism = synthetic construct
modified_base      1
                    mod_base = OTHER
                    note = 2'-fluorouridine phosphorothioate
modified_base      2
                    mod_base = OTHER
                    note = 2'-fluoroguanosine phosphorothioate
modified_base      3
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      4
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      5
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      6
                    mod_base = OTHER
                    note = 2'-fluoroguanosine
modified_base      7
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base      8
                    mod_base = OTHER
                    note = 2'-O-methyladenosine
modified_base      9
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     10
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     11
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     12
                    mod_base = OTHER
                    note = 2'-O-methylcytidine
modified_base     13
                    mod_base = OTHER
                    note = 2'-O-methyluridine
modified_base     14
                    mod_base = OTHER
                    note = 2'-fluorouridine
modified_base     15
                    mod_base = OTHER

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-continued

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modified_base      note = 2'-O-methylguanosine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine
                   17
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   18
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   19
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine phosphorothioate
                   20
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine phosphorothioate
                   21
                   mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 278
tgcaagcacc ccttgccct t                                     21

SEQ ID NO: 279      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine phosphorothioate
                   2
                   mod_base = OTHER
modified_base      note = 2'-fluoroguanosine phosphorothioate
                   3
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   4
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   5
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   6
                   mod_base = OTHER
modified_base      note = 2'-fluoroadenosine
                   7
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   8
                   mod_base = OTHER
modified_base      note = 2'-O-methylguanosine
                   9
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   10
                   mod_base = OTHER
modified_base      note = 2'-O-methyladenosine
                   11
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   12
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   13
                   mod_base = OTHER
modified_base      note = 2'-O-methylcytidine
                   14
                   mod_base = OTHER
modified_base      note = 2'-fluorocytidine
                   15
                   mod_base = OTHER
modified_base      note = 2'-O-methyluridine
                   16
                   mod_base = OTHER
modified_base      note = 2'-fluorouridine
                   17

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-continued

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modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
18
modified_base      mod_base = OTHER
                   note = 2'-O-methylguanosine
19
modified_base      mod_base = OTHER
                   note = 2'-O-methylcytidine phosphorothioate
20
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine phosphorothioate
21
modified_base      mod_base = OTHER
                   note = 2'-O-methyluridine
SEQUENCE: 279
tgcgcaagca ccccttgct t                               21

SEQ ID NO: 280      moltype = RNA length = 21
FEATURE            Location/Qualifiers
source             1..21
                   mol_type = other RNA
                   organism = synthetic construct
modified_base      1
                   mod_base = OTHER
                   note = 2'-fluorouridine phosphorothioate
modified_base      2
                   mod_base = OTHER
                   note = 2'-fluorocytidine phosphorothioate
modified_base      3
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      4
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      5
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      6
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      7
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      8
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      9
                   mod_base = OTHER
                   note = 2'-O-methyladenosine
modified_base      10
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      11
                   mod_base = OTHER
                   note = 2'-O-methylguanosine
modified_base      12
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      13
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      14
                   mod_base = OTHER
                   note = 2'-fluorouridine
modified_base      15
                   mod_base = OTHER
                   note = 2'-O-methyluridine
modified_base      16
                   mod_base = OTHER
                   note = 2'-fluoroguanosine
modified_base      17
                   mod_base = OTHER
                   note = 2'-O-methylcytidine
modified_base      18
                   mod_base = OTHER
                   note = 2'-O-methyladenosine

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-continued

modified_base	19	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	
modified_base	20	
	mod_base = OTHER	
	note = 2'-O-methyluridine phosphorothioate	
modified_base	21	
	mod_base = OTHER	
	note = 2'-O-methyluridine	
SEQUENCE: 280		
tcgccgggat gccttgcat t		21
SEQ ID NO: 281	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
source	1..9	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 281		
YTFTNYWMH		9
SEQ ID NO: 282	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 282		
EINPINGRSN YAQKFQG		17
SEQ ID NO: 283	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 283		
GTRAMHY		7
SEQ ID NO: 284	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 284		
EINPINGRSN YAEKFQG		17
SEQ ID NO: 285	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 285		
EINPIQGRSN YAEKFQG		17
SEQ ID NO: 286	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 286		
RTSENIYNNL A		11
SEQ ID NO: 287	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 287		
AATNLAD		7
SEQ ID NO: 288	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
source	1..9	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 288		
QHFwGTPLT		9

-continued

SEQ ID NO: 289	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 289		
AATNLAE		7
SEQ ID NO: 290	moltype = AA length = 10	
FEATURE	Location/Qualifiers	
source	1..10	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 290		
QHFWTPLTF		10
SEQ ID NO: 291	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 291		
RTSENIYSNL A		11
SEQ ID NO: 292	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 292		
AGTNLAD		7
SEQ ID NO: 293	moltype = AA length = 116	
FEATURE	Location/Qualifiers	
source	1..116	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 293		
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY		60
AQKFQGRVTL TVDTSSSTAY MELSR LRSDD TAVYYCARGT RAMHYWGQGT LVTVSS		116
SEQ ID NO: 294	moltype = AA length = 116	
FEATURE	Location/Qualifiers	
source	1..116	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 294		
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY		60
AEKFQGRVTL TVDTSSSTAY MELSR LRSDD TAVYYCARGT RAMHYWGQGT LVTVSS		116
SEQ ID NO: 295	moltype = AA length = 116	
FEATURE	Location/Qualifiers	
source	1..116	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 295		
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY		60
AEKFQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSS		116
SEQ ID NO: 296	moltype = AA length = 116	
FEATURE	Location/Qualifiers	
source	1..116	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 296		
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY		60
AEKFQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSS		116
SEQ ID NO: 297	moltype = AA length = 116	
FEATURE	Location/Qualifiers	
source	1..116	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 297		
QVQLQQGAE LVKPGASVKL SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY		60
GERFKTKATL TVDKSSSTAY MQLSSLTSED SAVYYCARGT RAMHYWGQGT SVTVSS		116

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SEQ ID NO: 298 moltype = AA length = 107
FEATURE Location/Qualifiers
source 1..107
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 298
DIQMTQSPSS LSASVGDVRT ITCRTSENIY NNLAWYQQKP GKSPKLLIYA ATNLADGVPS 60
RFSGSGSGTD YLTISSLQP EDFATYYCQH FWGTPLTFGG GTKVEIK 107

SEQ ID NO: 299 moltype = AA length = 107
FEATURE Location/Qualifiers
source 1..107
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 299
DIQMTQSPSS LSASVGDVRT ITCRTSENIY NNLAWYQQKP GKAPKLLIYA ATNLADGVPS 60
RFSGSGSGTD YLTISSLQP EDFATYYCQH FWGTPLTFGG GTKVEIK 107

SEQ ID NO: 300 moltype = AA length = 107
FEATURE Location/Qualifiers
source 1..107
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 300
DIQMTQSPSS LSASVGDVRT ITCRTSENIY NNLAWYQQKP GKAPKLLIYA ATNLAEVPS 60
RFSGSGSGTD YLTISSLQP EDFATYYCQH FWGTPLTFGG GTKVEIK 107

SEQ ID NO: 301 moltype = AA length = 107
FEATURE Location/Qualifiers
source 1..107
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 301
DIQMTQSPSS LSASVGDVRT ITCRTSENIY SNLAWYQQKP GKAPKLLIYA GTNLADGVPS 60
RFSGSGSGTD YLTISSLQP EDFANYCQH FWGTPLTFGG GTKVEIK 107

SEQ ID NO: 302 moltype = AA length = 107
FEATURE Location/Qualifiers
source 1..107
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 302
DIQMTQSPAS LSVSVGETVT ITCRTSENIY NNLAWYQQKQ GKSPQLLVYA ATNLADGVPS 60
RFSGSGSGTQ YSLKINSLQS EDFGNYYCQH FWGTPLTFGA GTKLELK 107

SEQ ID NO: 303 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 303
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AQKFQGRVTL TVDTSISTAY MELSRLRSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PELLGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTI SKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQDPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 304 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 304
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AQKFQGRVTL TVDTSISTAY MELSRLRSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PEAGGSPVF 240
LFPPKPKDTL MISRTPEVTC VVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTI SKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQDPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

-continued

SEQ ID NO: 305 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 305
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWGMGE INPINGRSNY 60
AQKFQGRVTL TVDTSISTAY MELSRRLRSD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC GVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 306 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 306
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWGMGE INPINGRSNY 60
AQKFQGRVTL TVDTSISTAY MELSRRLRSD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 307 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 307
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWGMGE INPINGRSNY 60
AQKFQGRVTL TVDTSISTAY MELSRRLRSD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALGAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 308 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 308
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWGMGE INPINGRSNY 60
AQKFQGRVTL TVDTSISTAY MELSRRLRSD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PELLGGGPSVF 240
LFPKPKDTL MISRTPEVTC VVAVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYGSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 309 moltype = AA length = 445
FEATURE Location/Qualifiers
source 1..445
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 309
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY 60
AEKFQGRVTL TVDTSSTAY MELSRRLRSD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PELLGGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 310 moltype = AA length = 445

-continued

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FEATURE                               Location/Qualifiers
source                                 1..445
                                         mol_type = protein
                                         organism = synthetic construct

SEQUENCE: 310
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSRRLSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 311             moltype = AA length = 445
FEATURE                               Location/Qualifiers
source                                 1..445
                                         mol_type = protein
                                         organism = synthetic construct

SEQUENCE: 311
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSRRLSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VSVLTVLHQ DWLNGKEYKC GVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 312             moltype = AA length = 445
FEATURE                               Location/Qualifiers
source                                 1..445
                                         mol_type = protein
                                         organism = synthetic construct

SEQUENCE: 312
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSRRLSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 313             moltype = AA length = 445
FEATURE                               Location/Qualifiers
source                                 1..445
                                         mol_type = protein
                                         organism = synthetic construct

SEQUENCE: 313
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSRRLSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PEAAGGPSVF 240
LFPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VSVLTVLHQ DWLNGKEYKC KVSNKALGAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 314             moltype = AA length = 445
FEATURE                               Location/Qualifiers
source                                 1..445
                                         mol_type = protein
                                         organism = synthetic construct

SEQUENCE: 314
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWIGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSRRLSDD TAVYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKTSTGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPPCPA PELGGGPSVF 240
LFPKPKDTL MISRTPEVTC VVAVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYGSTYR 300
VSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTI SKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 315             moltype = AA length = 445
FEATURE                               Location/Qualifiers

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-continued

```

source                1..445
                      mol_type = protein
                      organism = synthetic construct

SEQUENCE: 315
QVQLVQSGAE VVKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PELLGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTIKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQOGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 316        moltype = AA length = 445
FEATURE              Location/Qualifiers
source                1..445
                      mol_type = protein
                      organism = synthetic construct

```

```

SEQUENCE: 316
QVQLVQSGAE VVKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTIKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQOGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 317        moltype = AA length = 445
FEATURE              Location/Qualifiers
source                1..445
                      mol_type = protein
                      organism = synthetic construct

```

```

SEQUENCE: 317
QVQLVQSGAE VVKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTIKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQOGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 318        moltype = AA length = 445
FEATURE              Location/Qualifiers
source                1..445
                      mol_type = protein
                      organism = synthetic construct

```

```

SEQUENCE: 318
QVQLVQSGAE VVKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTIKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQOGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 319        moltype = AA length = 445
FEATURE              Location/Qualifiers
source                1..445
                      mol_type = protein
                      organism = synthetic construct

```

```

SEQUENCE: 319
QVQLVQSGAE VVKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALGAP IEKTIKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQOGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 320        moltype = AA length = 445
FEATURE              Location/Qualifiers
source                1..445

```

-continued

```

mol_type = protein
organism = synthetic construct
SEQUENCE: 320
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPIQGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PELLGGPSVF 240
LFPKPDKDTL MISRTPEVTC VVVAVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYGSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 321      moltype = AA length = 445
FEATURE           Location/Qualifiers
source            1..445
                 mol_type = protein
                 organism = synthetic construct

```

```

SEQUENCE: 321
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PELLGGPSVF 240
LFPKPDKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 322      moltype = AA length = 445
FEATURE           Location/Qualifiers
source            1..445
                 mol_type = protein
                 organism = synthetic construct

```

```

SEQUENCE: 322
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPKPDKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 323      moltype = AA length = 445
FEATURE           Location/Qualifiers
source            1..445
                 mol_type = protein
                 organism = synthetic construct

```

```

SEQUENCE: 323
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPKPDKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 324      moltype = AA length = 445
FEATURE           Location/Qualifiers
source            1..445
                 mol_type = protein
                 organism = synthetic construct

```

```

SEQUENCE: 324
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCCPPCPA PEAAGGPSVF 240
LFPKPDKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSDIAVEW ESNQGPENNY KTTTPVLDSD GSFFLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

```

```

SEQ ID NO: 325      moltype = AA length = 445
FEATURE           Location/Qualifiers
source            1..445
                 mol_type = protein

```

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```

                                organism = synthetic construct
SEQUENCE: 325
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPCPPA PEAAGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALGAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSTIAVEW ESNQGPENNY KTTPPVLDSG GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 326      moltype = AA length = 445
FEATURE           Location/Qualifiers
source            1..445
                  mol_type = protein
                  organism = synthetic construct

SEQUENCE: 326
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWMHWVRQA PGQGLEWMGE INPINGRSNY 60
AEKFGQGRVTL TVDTSSSTAY MELSSLRSED TATYYCARGT RAMHYWGQGT LVTVSSASTK 120
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS 180
LSSVTVTPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KHTCPCPPA PELLGGPSVF 240
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYGSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSREEMTKN 360
QVSLTCLVKG FYPSTIAVEW ESNQGPENNY KTTPPVLDSG GSFPLYSKLT VDKSRWQQGN 420
VFSCSVMHEA LHNHYTQKSL SLSPG 445

SEQ ID NO: 327      moltype = AA length = 214
FEATURE           Location/Qualifiers
source            1..214
                  mol_type = protein
                  organism = synthetic construct

SEQUENCE: 327
DIQMTQSPSS LSASVGRVIT ITCRTSENIY NNLAWYQQKP GKSPKLLIYA ATNLADGVPS 60
RFGSGSGSDT YTLTISSLQP EDFATYYCQH FWGTPLTFGG GTKVEIKRTV AAPSVFIFPP 120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSLSTLT 180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214

SEQ ID NO: 328      moltype = AA length = 214
FEATURE           Location/Qualifiers
source            1..214
                  mol_type = protein
                  organism = synthetic construct

SEQUENCE: 328
DIQMTQSPSS LSASVGRVIT ITCRTSENIY NNLAWYQQKP GKAPKLLIYA ATNLADGVPS 60
RFGSGSGSDT YTLTISSLQP EDFATYYCQH FWGTPLTFGG GTKVEIKRTV AAPSVFIFPP 120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSLSTLT 180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214

SEQ ID NO: 329      moltype = AA length = 214
FEATURE           Location/Qualifiers
source            1..214
                  mol_type = protein
                  organism = synthetic construct

SEQUENCE: 329
DIQMTQSPSS LSASVGRVIT ITCRTSENIY NNLAWYQQKP GKAPKLLIYA ATNLAEVPS 60
RFGSGSGSDT YTLTISSLQP EDFATYYCQH FWGTPLTFGG GTKVEIKRTV AAPSVFIFPP 120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSLSTLT 180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214

SEQ ID NO: 330      moltype = AA length = 214
FEATURE           Location/Qualifiers
source            1..214
                  mol_type = protein
                  organism = synthetic construct

SEQUENCE: 330
DIQMTQSPSS LSASVGRVIT ITCRTSENIY SNLAWYQQKP GKAPKLLIYA GTNLADGVPS 60
RFGSGSGSDT YTLTISSLQP EDFANYCQH FWGTPLTFGG GTKVEIKRTV AAPSVFIFPP 120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSLSTLT 180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC 214

SEQ ID NO: 331      moltype = AA length = 24
FEATURE           Location/Qualifiers
source            1..24
                  mol_type = protein
                  organism = synthetic construct

SEQUENCE: 331

```

-continued

CGIFGEIEEL IEEGLENLID WGNA	24
SEQ ID NO: 332	moltype = AA length = 24
FEATURE	Location/Qualifiers
source	1..24
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 332	
GLFEAIEGFI ENGWEGMIDG WYGC	24
SEQ ID NO: 333	moltype = AA length = 27
FEATURE	Location/Qualifiers
source	1..27
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 333	
GLFEAIEGFI ENGWEGMIWD YGSGSCG	27
SEQ ID NO: 334	moltype = AA length = 23
FEATURE	Location/Qualifiers
source	1..23
	mol_type = protein
	organism = synthetic construct
SITE	23
	note = Glycine hexaethylene glycol amide
SEQUENCE: 334	
GLFEAIEGFI ENGWEGMIDG WYG	23
SEQ ID NO: 335	moltype = AA length = 27
FEATURE	Location/Qualifiers
source	1..27
	mol_type = protein
	organism = synthetic construct
CARBOHYD	27
	note = Lysine N-linked
	N-acetylgalactosaminyl- (1-3) -N-acetylgalactosamine
SEQUENCE: 335	
GLFEAIEGFI ENGWEGMIWD YGSGSCK	27
SEQ ID NO: 336	moltype = AA length = 27
FEATURE	Location/Qualifiers
source	1..27
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 336	
CLIGAILKVL ATGLPTLISW IKNRKQ	27
SEQ ID NO: 337	moltype = AA length = 26
FEATURE	Location/Qualifiers
source	1..26
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 337	
GIGAVLKVLT TGLPALISWI KKRQQ	26
SEQ ID NO: 338	moltype = AA length = 13
FEATURE	Location/Qualifiers
source	1..13
	mol_type = protein
	organism = synthetic construct
SITE	13
	note = Phenylalanine amide
SEQUENCE: 338	
IFGAIAGLLK NIF	13
SEQ ID NO: 339	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 339	
FFGHLFKLAT KIIPSLFQ	18
SEQ ID NO: 340	moltype = AA length = 21
FEATURE	Location/Qualifiers
source	1..21

-continued

	mol_type = protein organism = synthetic construct	
SEQUENCE: 340 KETWWETWWT EWSQPKKKRK V		21
SEQ ID NO: 341 FEATURE source	moltype = AA length = 19 Location/Qualifiers 1..19 mol_type = protein organism = synthetic construct	
SEQUENCE: 341 LLIILRRRRI RKQAHHSK		19
SEQ ID NO: 342 FEATURE source	moltype = AA length = 26 Location/Qualifiers 1..26 mol_type = protein organism = synthetic construct	
SEQUENCE: 342 DPKGDPKGVT VTVTVTVTKG GPKPD		26
SEQ ID NO: 343 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 343 CSIPPEVKFN KPFVYLI		17
SEQ ID NO: 344 FEATURE source	moltype = AA length = 27 Location/Qualifiers 1..27 mol_type = protein organism = synthetic construct	
SEQUENCE: 344 GWTLSAGYL LGKINLKALA ALAKKIL		27
SEQ ID NO: 345 FEATURE source	moltype = AA length = 21 Location/Qualifiers 1..21 mol_type = protein organism = synthetic construct	
SEQUENCE: 345 AGYLLGKINL KALAALAKKI L		21
SEQ ID NO: 346 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 346 GALFLGFLGA AGSTMGA		17
SEQ ID NO: 347 FEATURE source	moltype = AA length = 20 Location/Qualifiers 1..20 mol_type = protein organism = synthetic construct	
SEQUENCE: 347 HGLASTLTRW AHYNALIRAF		20
SEQ ID NO: 348 FEATURE source	moltype = AA length = 20 Location/Qualifiers 1..20 mol_type = protein organism = synthetic construct	
SEQUENCE: 348 GLWRALWRLL RSLWRLLWRA		20
SEQ ID NO: 349 FEATURE source	moltype = AA length = 30 Location/Qualifiers 1..30 mol_type = protein organism = synthetic construct	
SEQUENCE: 349 WEAALAEALA EALAEHLAEA LAEALALAA		30

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SEQ ID NO: 359	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
source	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 359		
GRKKRRQRRR PPQ		13
SEQ ID NO: 360	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 360		
LLIILRRRIR KQAHASK		18
SEQ ID NO: 361	moltype = AA length = 27	
FEATURE	Location/Qualifiers	
source	1..27	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 361		
GWTLNSAGYL LGKINLKALA ALAKKIL		27
SEQ ID NO: 362	moltype = AA length = 27	
FEATURE	Location/Qualifiers	
source	1..27	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 362		
GALFLGFLGA AGSTMGAWSQ PPKKRKV		27
SEQ ID NO: 363	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 363		
KETWWETWWT EWSQPKKKRK V		21
SEQ ID NO: 364	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
source	1..12	
	mol_type = protein	
	organism = synthetic construct	
VARIANT	1..12	
	note = This sequence may encompass 6-12 residues	
SEQUENCE: 364		
RRRRRRRRRR RR		12
SEQ ID NO: 365	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 365		
KLALKLALKA LKAALKLA		18
SEQ ID NO: 366	moltype = AA length = 9	
FEATURE	Location/Qualifiers	
source	1..9	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 366		
RRWRRWRR		9
SEQ ID NO: 367	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
source	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 367		
CGYGPKKKRK VGG		13
SEQ ID NO: 368	moltype = AA length = 8	

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FEATURE source	Location/Qualifiers 1..8 mol_type = protein organism = synthetic construct	
SEQUENCE: 368 KKKKKKKK		8
SEQ ID NO: 369 FEATURE source	moltype = AA length = 22 Location/Qualifiers 1..22 mol_type = protein organism = synthetic construct	
SEQUENCE: 369 MVRRLVTLR IRRACGPPRV RV		22
SEQ ID NO: 370 FEATURE source	moltype = AA length = 28 Location/Qualifiers 1..28 mol_type = protein organism = synthetic construct	
SEQUENCE: 370 LSTAADMQGV VTDGMASGLD KDYLKPPDD		28
SEQ ID NO: 371 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 371 ctgcctctcc accagccca		19
SEQ ID NO: 372 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 372 tgggctggtg gagaggcag		19
SEQ ID NO: 373 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 373 gcagagatgg agagaggaa		19
SEQ ID NO: 374 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 374 ttcctctctc catctctgc		19
SEQ ID NO: 375 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 375 gcggtttcct ccgggacaa		19
SEQ ID NO: 376 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 376 ttgtcccgga ggaaaccgc		19
SEQ ID NO: 377 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	

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SEQUENCE: 377		
ggacgacgga ggcgtgatt		19
SEQ ID NO: 378	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 378		
aatcacgcct ccgtcgtcc		19
SEQ ID NO: 379	moltype = DNA length = 25	
FEATURE	Location/Qualifiers	
source	1..25	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 379		
cgggcacccg gaaacatgca gggaa		25
SEQ ID NO: 380	moltype = DNA length = 25	
FEATURE	Location/Qualifiers	
source	1..25	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 380		
ttccctgcat gtttcgggt gcccg		25
SEQ ID NO: 381	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 381		
ccgaaacat gcagggaag		19
SEQ ID NO: 382	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 382		
cttcctgca tgttccgg		19
SEQ ID NO: 383	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 383		
gaaatgaacg agagccaca		19
SEQ ID NO: 384	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 384		
tgtggctctc gttcatttc		19
SEQ ID NO: 385	moltype = DNA length = 25	
FEATURE	Location/Qualifiers	
source	1..25	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 385		
tggcacactc aagactccca cggag		25
SEQ ID NO: 386	moltype = DNA length = 25	
FEATURE	Location/Qualifiers	
source	1..25	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 386		
ctccgtggga gtcttgagtg tgcca		25
SEQ ID NO: 387	moltype = DNA length = 19	

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FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 387		
ccacggaggt tcagttcca		19
SEQ ID NO: 388	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 388		
tggaaactgaa cctccgtgg		19
SEQ ID NO: 389	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 389		
accaccacca ccaccacca		19
SEQ ID NO: 390	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 390		
tggtggtggt ggtggtggt		19
SEQ ID NO: 391	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 391		
cgccattcat gaaggggtg		19
SEQ ID NO: 392	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 392		
cacccttca tgaatggcg		19
SEQ ID NO: 393	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 393		
catgaagggg tggagcctg		19
SEQ ID NO: 394	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 394		
caggctccac cccttcatg		19
SEQ ID NO: 395	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 395		
gagcctgett tgagcggaa		19
SEQ ID NO: 396	moltype = DNA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = other DNA	
	organism = synthetic construct	

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SEQUENCE: 396 ttccgctcaa agcaggctc		19
SEQ ID NO: 397 FEATURE source	moltype = DNA length = 25 Location/Qualifiers 1..25 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 397 ccgagccttt gagaaggatc gcttt		25
SEQ ID NO: 398 FEATURE source	moltype = DNA length = 25 Location/Qualifiers 1..25 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 398 aaagcgatcc ttctcaaagg ctg		25
SEQ ID NO: 399 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 399 ggcagggcgc ccgcgagg		19
SEQ ID NO: 400 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 400 cctgcgggg cgccctgcc		19
SEQ ID NO: 401 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 401 gatgattagt tcagagata		19
SEQ ID NO: 402 FEATURE source	moltype = DNA length = 19 Location/Qualifiers 1..19 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 402 tatctctgaa ctaatcatc		19
SEQ ID NO: 403 FEATURE source	moltype = AA length = 4 Location/Qualifiers 1..4 mol_type = protein organism = synthetic construct	
SEQUENCE: 403 GGFG		4
SEQ ID NO: 404 FEATURE source	moltype = AA length = 4 Location/Qualifiers 1..4 mol_type = protein organism = synthetic construct	
SEQUENCE: 404 ALAL		4
SEQ ID NO: 405 FEATURE source	moltype = AA length = 4 Location/Qualifiers 1..4 mol_type = protein organism = synthetic construct	
SEQUENCE: 405 GFLG		4
SEQ ID NO: 406	moltype = AA length = 17	

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FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = synthetic construct	
VARIANT	6	
	note = N or Q	
VARIANT	13	
	note = Q or E	
SEQUENCE: 406		
EINPIXGRSN YAXKFQG		17
SEQ ID NO: 407	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
source	1..11	
	mol_type = protein	
	organism = synthetic construct	
VARIANT	8	
	note = N or S	
SEQUENCE: 407		
RTSENIYXNL A		11
SEQ ID NO: 408	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
VARIANT	2	
	note = A or G	
VARIANT	7	
	note = D or E	
SEQUENCE: 408		
AXTNLAX		7
SEQ ID NO: 409	moltype = AA length = 10	
FEATURE	Location/Qualifiers	
source	1..10	
	mol_type = protein	
	organism = synthetic construct	
VARIANT	10	
	note = F or absent	
SEQUENCE: 409		
QHFWGTPLTX		10
SEQ ID NO: 410	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
VARIANT	7	
	note = D or E	
SEQUENCE: 410		
AATNLAX		7

1. A polynucleotide-antibody conjugate comprising an anti-transferrin receptor antibody or antigen binding fragment thereof conjugated to a polynucleotide, wherein the polynucleotide is from 19 to 30 nucleotides in length and wherein the polynucleotide mediates RNA interference against DUX4 mRNA and downregulation of DUX4 biomarker mRNA level.

2. The polynucleotide-antibody conjugate of claim 1, wherein the polynucleotide is a single stranded polynucleotide.

3. The polynucleotide-antibody conjugate of claim 2, wherein the single stranded polynucleotide is an antisense oligonucleotide (ASO) or a phosphorodiamidate morpholino oligomers (PMO).

4. The polynucleotide-antibody conjugate of claim 1, wherein the anti-transferrin receptor antibody or antigen binding fragment thereof binds to a transferrin receptor on a cell surface of a muscle cell.

5. The polynucleotide-antibody conjugate of claim 1, wherein the polynucleotide comprises at least one 2' modified nucleotide, at least one modified internucleotide linkage, or at least one inverted abasic moiety.

6. The polynucleotide-antibody conjugate of claim 1, wherein the polynucleotide hybridizes to at least 8 contiguous bases of the target sequence of a human DUX4 mRNA.

7. The polynucleotide-antibody conjugate of claim 1, wherein the polynucleotide is from 19 to 25 nucleotides in length.

8. The polynucleotide-antibody conjugate of claim 1, wherein the polynucleotide comprises a sequence selected from a group consisting of SEQ ID NOs: 72, 76, 126, 131, 132, 134, 135, 136, 212, 216, 266, 271, 272, 274, 275, and 276.

9. The polynucleotide-antibody conjugate of claim 1, wherein the polynucleotide-antibody conjugate comprises a

linker connecting the anti-transferrin receptor antibody or antigen binding fragment thereof to the polynucleotide.

10. The polynucleotide-antibody conjugate of claim **5**, wherein the at least one 2' modified nucleotide comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-amino-propyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-ODMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA) modified nucleotide, locked nucleic acid (LNA), ethylene nucleic acid (ENA), or a combination thereof.

11. The polynucleotide-antibody conjugate of claim **5**, wherein the at least one modified internucleotide linkage comprises a phosphorothioate linkage or a phosphorodithioate linkage.

12. The polynucleotide-antibody conjugate of claim **5**, wherein the polynucleotide comprises three or more 2' modified nucleotides selected from 2'-O-methyl modified nucleotide and 2'-deoxy-2'-fluoro modified nucleotide.

13. The polynucleotide-antibody conjugate of claim **1**, wherein the polynucleotide-antibody conjugate has a polynucleotide to antibody ratio from 1 to 4.

14. The polynucleotide-antibody conjugate of claim **1**, wherein the polynucleotide comprises a 5'-terminal vinylphosphonate modified nucleotide.

15. The polynucleotide-antibody conjugate of claim **1**, wherein the polynucleotide-antibody conjugate is formulated for parenteral administration.

16. The polynucleotide-antibody conjugate of claim **1**, wherein the downregulation of DUX4 biomarker mRNA level is evaluated by expression level of one or more DUX4 biomarker genes selected from a group consisting of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX.

17. The polynucleotide-antibody conjugate of claim **1**, wherein the anti-transferrin receptor antibody or antigen binding fragment thereof is conjugated to the 5' end of the polynucleotide.

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