

TREATMENT OF FGG RELATED DISEASES AND DISORDERS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional No. 63/286,393, filed December 6, 2021, which application is incorporated herein by reference.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 54462-736601.xml, created December 3, 2022, which is 5155 kilobytes in size. The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

BACKGROUND

[0003] Psychiatric and neurological diseases are widely abundant, and may affect a wide variety of people. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0004] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets fibrinogen gamma gene (FGG). Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets FGG and when administered to a subject in an effective amount improves a mental disorder measurement of a mental disorder. In some embodiments, the mental disorder comprises a psychiatric disorder. In some embodiments, the psychiatric disorder comprises a depressive disorder (e.g., major depressive disorder, persistent depressive disorder, treatment resistant depression and signs or symptoms of depression), post-traumatic stress disorder, mood disorder, anxiety disorder, eating disorder, substance-use disorder, bipolar disorder, personality disorder, schizophrenia, or schizoaffective disorder. In some embodiments, the mental disorder measurement is chosen from the group consisting of a Montgomery-Asberg Depression Rating Scale (MADRS) score, a Hamilton Depression Rating Scale-17 score, anxiety signs and symptoms, eating disorder signs and symptoms, substance-use disorder signs and symptoms, post-traumatic stress disorder signs and symptoms, bipolar disorder signs and symptoms, schizophrenia signs and symptoms, and psychosis signs and symptoms. In some embodiments, the mental disorder comprises a neurological disorder. In some embodiments, the neurological disorder comprises Alzheimer's disease, dementia, delirium, cognitive decline, vascular dementia, headache (e.g., migraine), chronic pain (e.g., fibromyalgia), chronic fatigue syndrome (e.g. myalgic encephalomyelitis), or motor neuron disease (e.g., amyotrophic lateral sclerosis). In some embodiments, the mental disorder measurement is chosen from the group consisting of cognitive function, CNS amyloid plaques, CNS tau accumulation, CSF beta-amyloid 42, CSF tau, CSF phospho-tau, Lewy bodies, CSF alpha-synuclein, headache symptoms or signs, migraine symptoms or signs, chronic pain symptoms or signs, fibromyalgia symptoms or signs, chronic fatigue syndrome (e.g. myalgic encephalomyelitis) symptoms or signs, and

motor neuron disease (e.g., amyotrophic lateral sclerosis) symptoms or signs. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises a modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof. In some embodiments, the modified nucleoside comprises one or more 2' fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 modified nucleosides. In some embodiments, the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α -tocopherol, or a combination thereof. In some embodiments, the oligonucleotide comprises a sugar moiety attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the sugar comprises N-acetylgalactosamine (GalNAc), N-acetylglucosamine (GlcNAc), or mannose. The sugar moiety may comprise ETL17. In some embodiments, the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand. In some embodiments, the sense strand is 12-30 nucleosides in length. In some embodiments, the antisense strand is 12-30 nucleosides in length. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 3621. In some embodiments, any one of the following is true with regard to the sense strand: all purines comprise 2' fluoro modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines; all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines; all purines comprise 2' fluoro modified purines, and all pyrimidines comprise 2'-O-methyl modified pyrimidines; all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2'-O-methyl modified purines; all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all

purines comprise a mixture of 2' fluoro and 2'-O-methyl modified purines; or all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise 2'-O-methyl modified purines. In some embodiments, the sense strand comprises any one of modification patterns 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, or 29S. In some embodiments, any one of the following is true with regard to the antisense strand: all purines comprise 2' fluoro modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines; all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines; all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise 2' fluoro modified pyrimidines; all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2'-O-methyl modified purines; all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2'-O-methyl modified purines; or all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise 2' fluoro modified purines. In some embodiments, the antisense strand comprises any one of modification patterns 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 1-1742 or 3713-3748, or a sequence thereof having 1 or 2 substitutions, additions, or deletions; and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 1743-3484 or 3749-3784, or a sequence thereof having 1 or 2 substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 1-1742 or 3713-3748, and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 1743-3484 or 3749-3784. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3723, 3724, 3726, or 3747, or a sequence thereof having 1 or 2 substitutions, additions, or deletions; and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3759, 3760, 3762, or 3783, or a sequence thereof having 1 or 2 substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3723, 3724, 3726, or 3747, and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3759, 3760, 3762, or 3783. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 352, 1003, 1011, or 1278, or a sequence thereof having 1 or 2 substitutions, additions, or deletions; and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 2094, 2745, 2753, or 3020, or a sequence thereof having 1 or 2 substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 352, 1003, 1011, or 1278, and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 2094, 2745, 2753, or 3020. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3591-3594, or a sequence thereof having 1 or 2 substitutions, additions, or deletions; and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3595-3598, or a sequence thereof having 1 or 2 substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3591-

3594, and the antisense strand comprises the nucleic acid sequence of any one of SEQ ID NOs: 3595-3598. In some embodiments, the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and a nucleoside sequence complementary to about 12-30 contiguous nucleosides of SEQ ID NO: 3621. Some embodiments include a pharmaceutically acceptable carrier. Disclosed herein, in some embodiments, are methods of treating a subject having a psychiatric disorder or a neurological disorder, comprising administering an effective amount of the composition to the subject. In some embodiments, the psychiatric disorder comprises a depressive disorder (e.g., major depressive disorder, persistent depressive disorder, treatment resistant depression and signs or symptoms of depression), post-traumatic stress disorder, mood disorder, anxiety disorders, eating disorder, substance-use disorder, bipolar disorder, personality disorder, schizophrenia, or a schizoaffective disorder. In some embodiments, the neurological disorder comprises Alzheimer's disease, dementia, delirium, cognitive decline, vascular dementia, headache (e.g., migraine), chronic pain (e.g., fibromyalgia), chronic fatigue syndrome (e.g. myalgic encephalomyelitis), and motor neuron disease (e.g., amyotrophic lateral sclerosis).

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] FIG. 1 is an example of a GalNAc ligand.

[0006] FIG. 2 is an example of a GalNAc ligand.

DETAILED DESCRIPTION

[0007] Large-scale human genetic data can improve the success rate of pharmaceutical discovery and development. A Genome Wide Association Study (GWAS) may detect associations between genetic variants and traits in a population sample. A GWAS may enable better understanding of the biology of disease, and provide applicable treatments. A GWAS can utilize genotyping and/or sequencing data, and often involves an evaluation of millions of genetic variants that are relatively evenly distributed across the genome. The most common GWAS design is the case-control study, which involves comparing variant frequencies in cases versus controls. If a variant has a significantly different frequency in cases versus controls, that variant is said to be associated with disease. Association statistics that may be used in a GWAS are p-values, as a measure of statistical significance; odds ratios (OR), as a measure of effect size; or beta coefficients (beta), as a measure of effect size. Researchers often assume an additive genetic model and calculate an allelic odds ratio, which is the increased (or decreased) risk of disease conferred by each additional copy of an allele (compared to carrying no copies of that allele). An additional concept in design and interpretation of GWAS is that of linkage disequilibrium, which is the non-random association of alleles. The presence of linkage disequilibrium can obfuscate which variant is "causal."

[0008] Functional annotation of variants and/or wet lab experimentation can identify the causal genetic variant identified via GWAS, and in many cases may lead to the identification of disease-causing genes. In particular, understanding the functional effect of a causal genetic variant (for example, loss of

protein function, gain of protein function, increase in gene expression, or decrease in gene expression) may allow that variant to be used as a proxy for therapeutic modulation of the target gene, or to gain insight into potential therapeutic efficacy and safety of a therapeutic that modulates that target.

[0009] Identification of such gene-disease associations has provided insights into disease biology and may be used to identify novel therapeutic targets for the pharmaceutical industry. In order to translate the therapeutic insights derived from human genetics, disease biology in patients may be exogenously ‘programmed’ into replicating the observation from human genetics. There are several potential options for therapeutic modalities that may be brought to bear in translating therapeutic targets identified via human genetics into novel medicines. These may include well established therapeutic modalities such as small molecules and monoclonal antibodies, maturing modalities such as oligonucleotides, and emerging modalities such as gene therapy and gene editing. The choice of therapeutic modality can depend on several factors including the location of a target (for example, intracellular, extracellular, or secreted), a relevant tissue (for example, liver, brain, or neural tissue) and a relevant indication.

[0010] The fibrinogen gamma chain gene, also known as fibrinogen gamma gene (FGG), is located on chromosome 4, and encodes fibrinogen gamma chain (also referred to as FGG protein). The FGG protein may be a gamma component of fibrinogen. FGG protein may include 453 amino acids and have a mass of about 51.5 kDa. An example of a FGG amino acid sequence, and further description of FGG is included at uniprot.org under accession no. P02679 (last modified September 29, 2021).

[0011] Here it is shown that genetic variants causing inactivation of FGG resulted in protective associations for psychiatric and neurological phenotypes. Therefore, inhibition of FGG may serve as a therapeutic for treatment of psychiatric diseases and disorders such as depressive disorder (e.g., major depressive disorder, persistent depressive disorder, treatment resistant depression, or signs and symptoms of depression), post-traumatic stress disorder (PTSD), mood disorders, anxiety disorders, eating disorders, substance-use disorders, bipolar disorder, personality disorders, schizophrenia and schizoaffective disorders, and neurological diseases and disorders such as Alzheimer’s disease, dementia, delirium, cognitive decline, vascular dementia, headache, migraine, chronic pain, fibromyalgia, chronic fatigue syndrome (e.g. myalgic encephalomyelitis (ME)), or motor neuron disease (e.g., amyotrophic lateral sclerosis).

[0012] Disclosed herein are compositions comprising an oligonucleotide that targets FGG. Where inhibition or targeting of FGG is disclosed, it is contemplated that some embodiments may include inhibiting or targeting a FGG protein or FGG RNA. For example, by inhibiting or targeting an RNA (e.g. mRNA) encoded by the FGG gene using an oligonucleotide described herein, the FGG protein may be inhibited or targeted as a result of there being less production of the FGG protein by translation of the FGG RNA; or a FGG protein may be targeted or inhibited by an oligonucleotide that binds or interacts with a FGG RNA and reduces production of the FGG protein from the FGG RNA. Thus, targeting FGG may refer to binding a FGG RNA and reducing FGG RNA or protein levels. The oligonucleotide may include a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO).

[0013] Also provided herein are methods of treating a mental disorder, such as a psychiatric disorder or neurological disorder or disease by providing or administering an oligonucleotide that targets FGG to a subject in need thereof. Administration of the oligonucleotide to a subject may improve psychiatric related traits, such as Montgomery-Asberg Depression Rating Scale (MADRS) (e.g. scale ranges from 0 to 60 with a higher score indicating worsening symptoms of depression), Hamilton Depression Rating Scale-17 (e.g. scale ranges from 0 to 52 with a higher score indicating worsening symptoms of depression), anxiety symptoms and signs, eating disorder symptoms and signs, substance-use disorder symptoms and signs, post-traumatic stress disorder symptoms and signs, bipolar disorder symptoms and signs, schizophrenia symptoms and signs, or psychosis symptoms and signs. Additionally, administration of the oligonucleotide to a subject may improve neurological related traits, such as Cognitive function, CNS amyloid plaques (e.g., accumulation), CNS tau accumulation, CSF beta-amyloid 42 (e.g., accumulation), CSF tau (e.g., accumulation), CSF phospho-tau (e.g., accumulation), Lewy bodies (e.g., accumulation), CSF alpha-synuclein (e.g., accumulation), headache symptoms and signs, migraine symptoms and signs, chronic pain symptoms and signs, fibromyalgia symptoms and signs, chronic fatigue syndrome (ME) symptoms and signs, or motor neuron disease (e.g. ALS) symptoms or signs.

I. COMPOSITIONS

[0014] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide. In some embodiments, the composition comprises an oligonucleotide that targets FGG. In some embodiments, the composition consists of an oligonucleotide that targets FGG. In some embodiments, the oligonucleotide reduces FGG mRNA expression in the subject. In some embodiments, the oligonucleotide reduces FGG protein expression in the subject. The oligonucleotide may include a small interfering RNA (siRNA) described herein. The oligonucleotide may include an antisense oligonucleotide (ASO) described herein. In some embodiments, a composition described herein is used in a method of treating a disorder in a subject in need thereof. Some embodiments relate to a composition comprising an oligonucleotide for use in a method of treating a disorder as described herein. Some embodiments relate to use of a composition comprising an oligonucleotide, in a method of treating a disorder (e.g., psychiatric or neurological) as described herein.

[0015] Some embodiments include a composition comprising an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases FGG mRNA or protein levels in a cell (e.g. hepatocyte or neuron), fluid (e.g., blood, serum, plasma, or cerebrospinal fluid (CSF)), tissue (e.g. brain or liver tissue), or organ (e.g., the brain or liver).

[0016] In some embodiments, the composition comprises an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases FGG mRNA levels in a cell or tissue. In some embodiments, the cell is a liver cell (e.g., hepatocyte). In some embodiments, the cell is a neuron. In some embodiments, the tissue is liver tissue. In some embodiments, the tissue is neural tissue. In some embodiments, the neural tissue is CNS tissue. In some embodiments, the neural tissue is brain tissue (e.g., neuronal, glia, or endothelial tissue). In some embodiments, the fluid is CSF. In some embodiments, the FGG mRNA levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as

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

[0017] In some embodiments, the composition comprises an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases FGG protein levels in a cell, fluid (e.g., CSF) or tissue. In some embodiments, the cell is a hepatocyte. In some embodiments, the cell is a neural cell (e.g., CNS cell (e.g., brain cell)). In some embodiments, the cell is a neuronal cell. In some embodiments, the cell is a glial cell. In some embodiments, the cell is an endothelial cell. In some embodiments, the tissue is liver tissue. In some embodiments, the tissue is neural (e.g., CNS (e.g., brain)) tissue. In some embodiments, the fluid is CSF. In some embodiments, the FGG protein levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the FGG protein levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the FGG protein levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the FGG protein levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the FGG protein levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the FGG protein levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the FGG protein levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0018] In some embodiments, the composition comprises an oligonucleotide that targets FGG and when administered to a subject in an effective amount diminishes a mental disorder or disease phenotype, such as a psychiatric disorder or neurological disorder phenotype. A disorder may include a disease. The psychiatric disease or disorder may include depressive disorder (e.g., major depressive disorder, persistent

depressive disorder, treatment resistant depression, or signs and symptoms of depression), post-traumatic stress disorder, mood disorders, anxiety disorders, eating disorders, substance-use disorders, bipolar disorder, personality disorders, schizophrenia and schizoaffective disorders. The neurological disease or disorder may include such as Alzheimer's disease, dementia, delirium, cognitive decline, vascular dementia, headache, migraine, chronic pain, fibromyalgia, chronic fatigue syndrome (e.g. myalgic encephalomyelitis (ME)), or motor neuron disease (e.g., amyotrophic lateral sclerosis). For psychiatric/neurological indications, fibrinogen may be lowered enough to have a therapeutic effect on mental disorders but without significantly affecting coagulation parameters such as PT or aPTT.

[0019] In some embodiments, the composition comprises an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases a psychiatric disease phenotype. The psychiatric disease phenotype may include a Montgomery-Asberg Depression Rating Scale (MADRS) score. The psychiatric disease phenotype may include a Hamilton Depression Rating Scale score. The psychiatric disease phenotype may include a sign or symptom of anxiety. The psychiatric disease phenotype may include a sign or symptom of an eating disorder. The psychiatric disease phenotype may include a sign or symptom of a substance-use disorder. The psychiatric disease phenotype may include a sign or symptom of post-traumatic stress disorder. The psychiatric disease phenotype may include a sign or symptom of bipolar disorder. The psychiatric disease phenotype may include a sign or symptom of schizophrenia. The psychiatric disease phenotype may include a sign or symptom of psychosis. In some embodiments, the psychiatric disease phenotype is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the psychiatric disease phenotype is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the psychiatric disease phenotype is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the psychiatric disease phenotype is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the psychiatric disease phenotype is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the psychiatric disease phenotype is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the psychiatric disease phenotype is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0020] In some embodiments, the composition comprises an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases a neurological disease phenotype. The neurological disease phenotype may include cognitive dysfunction. The neurological disease phenotype may include central nervous system (CNS) amyloid plaques. The neurological disease phenotype may include CNS tau accumulation. The neurological disease phenotype may include cerebrospinal fluid

(CSF) beta-amyloid 42. The neurological disease phenotype may include CSF tau. The neurological disease phenotype may include CSF phospho-tau. The neurological disease phenotype may include Lewy bodies. The neurological disease phenotype may include CSF alpha-synuclein. The neurological disease phenotype may include headache symptoms or signs. The neurological disease phenotype may include migraine symptoms or signs. The neurological disease phenotype may include chronic pain symptoms or signs. The neurological disease phenotype may include fibromyalgia symptoms or signs. The neurological disease phenotype may include chronic fatigue syndrome (e.g. myalgic encephalomyelitis) symptoms or signs. The neurological disease phenotype may include motor neuron disease (e.g., amyotrophic lateral sclerosis) symptoms or signs. In some embodiments, the neurological disease phenotype is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the neurological disease phenotype is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the neurological disease phenotype is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the neurological disease phenotype is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the neurological disease phenotype is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the neurological disease phenotype is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the neurological disease phenotype is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0021] The composition may treat a clotting or coagulation disorder. The composition may treat thrombophilia. The composition may affect clotting or a clotting time. In some embodiments, the composition comprises an oligonucleotide that decreases Fibrinogen. In some cases, a FGG siRNA composition may be useful as an anticoagulant, such as for treatment or prophylaxis of a coagulation or clotting disorders (e.g. venous thromboembolism, atrial fibrillation), given that significant FGG knockdown may lead to a prolonged clotting time (e.g. PT, INR or aPTT). For coagulation or clotting disorders, it is useful to lower Fibrinogen significantly enough to prolong clotting times to clinically meaningful levels for these indications. Provided herein are data that show FGG siRNA administration may result in FGG knockdown. FGG knockdown may result in decreased circulating fibrinogen. Decreased circulating fibrinogen may result in increased PT, INR and aPTT. As such, the compounds may be useful for reducing clotting. Some aspects relate to a composition comprising an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases fibrinogen.

[0022] In some embodiments, the prothrombin time (PT), International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) levels are unchanged as compared to administration. In

some embodiments, PT, INR or aPTT increases by no more than about 10%, as compared to prior to administration. In some embodiments, PT, INR or aPTT increase by no more than about 20%, no more than about 40%, no more than about 80%, no more than about 160%, no more than about 200%, no more than about 300%, no more than about 400%, or no more than about 600%, as compared to prior to administration. In some embodiments, the PT, INR or aPTT increases by 5%, 10%, 20%, 40%, 80%, 100%, 200%, 400% or 600%, or by a range defined by any of the two aforementioned percentages.

A. siRNAs

[0023] In some embodiments, the composition comprises an oligonucleotide that targets FGG, wherein the oligonucleotide comprises a small interfering RNA (siRNA). In some embodiments, the composition comprises an oligonucleotide that targets FGG, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand.

[0024] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand is 12-30 nucleosides in length. In some embodiments, the composition comprises a sense strand that is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. The sense strand may be 14-30 nucleosides in length. In some embodiments, the composition comprises an antisense strand is 12-30 nucleosides in length. In some embodiments, the composition comprises an antisense strand that is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. The antisense strand may be 14-30 nucleosides in length.

[0025] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of a full-length human FGG mRNA sequence such as SEQ ID NO: 3621. In SEQ ID NO: 3621, thymine (T) may be replaced with Uracil (U). In some embodiments, at least one of the sense strand and the antisense strand comprise a nucleoside sequence comprising at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of SEQ ID NO: 3621.

[0026] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a double-stranded RNA duplex. In some embodiments, the first base pair of the double-stranded RNA duplex is an AU base pair.

[0027] In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In

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

[0028] In some embodiments, the antisense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides.

[0029] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 19mer in a human FGG mRNA. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a human FGG mRNA.

[0030] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 17mer in a non-human primate FGG mRNA. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a non-human primate FGG mRNA.

[0031] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a human FGG mRNA and less than or equal to 20 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 10 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 30 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 40 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 50 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 10 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 20 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 30 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA

and less than or equal to 40 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human FGG mRNA and less than or equal to 50 human off-targets, with no more than 3 mismatches in the antisense strand.

[0032] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, siRNA binds with a human FGG mRNA target site that does not harbor an SNP, with a minor allele frequency (MAF) greater or equal to 1% (pos. 2-18). In some embodiments, the MAF is greater or equal to about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20%.

[0033] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1742, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1742, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the sense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1742, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1742. In any of SEQ ID NOs: 1-1742, thymine (T) may be replaced with Uracil (U).

[0034] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1743-3484, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand sequence comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1743-3484 or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or

deletions. In some embodiments, the antisense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1743-3484, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1743-3484. In any of SEQ ID NOs: 1743-3484, thymine (T) may be replaced with Uracil (U).

[0035] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3713-3748, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3713-3748, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the sense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3713-3748, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3713-3748. In any of SEQ ID NOs: 3713-3748, thymine (T) may be replaced with Uracil (U).

[0036] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an

antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3749-3784, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand sequence comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3749-3784 or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3749-3784, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3749-3784. In any of SEQ ID NOs: 3749-3784, thymine (T) may be replaced with Uracil (U).

[0037] In some embodiments, the sense and/or antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to a sense and/or antisense strand sequence in any of **Tables 3-7**. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any **Tables 3-7**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any **Tables 3-7**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any **Tables 3-7**. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) FGG mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0038] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0039] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0040] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0041] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0042] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0043] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset G, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset G, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset G. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0044] In some embodiments, the sense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOs: 352, 1003, 1011, or 1278. In some embodiments, the

sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 352, 1003, 1011, or 1278, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 352, 1003, 1011, or 1278, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 352, 1003, 1011, or 1278. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0045] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 352. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 352, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 352, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 352. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0046] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 1003. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1003, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1003, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1003. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0047] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 1011. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1011, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1011, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1011. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0048] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 1278. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1278, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions,

or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1278, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 1278. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0049] In some embodiments, the antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOS: 2094, 2745, 2753, or 3020. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 2094, 2745, 2753, or 3020, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 2094, 2745, 2753, or 3020, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 2094, 2745, 2753, or 3020. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with a sense strand). The antisense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end or 3' end).

[0050] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 2094. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2094, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2094, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2094. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0051] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 2745. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2745, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2745, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2745. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0052] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 2753. In some embodiments, the antisense strand comprises the nucleoside

sequence of SEQ ID NO: 2753, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2753, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 2753. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0053] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3020. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3020, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3020, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3020. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0054] In some embodiments, the sense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOS: 3723, 3724, 3726, or 3747. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3723, 3724, 3726, or 3747, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3723, 3724, 3726, or 3747, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3723, 3724, 3726, or 3747. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0055] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3723. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3723, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3723, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3723. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0056] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3724. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3724, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3724, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3724. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0057] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3726. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3726, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3726, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3726. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0058] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3747. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3747, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3747, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3747. The sense strand may include any internucleoside linkages or nucleoside modifications described herein. The sense strand may include an overhang (e.g. 2 bases on a 5' or 3' end when paired with an antisense strand). The sense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end).

[0059] In some embodiments, the antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOS: 3759, 3760, 3762, or 3783. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3759, 3760, 3762, or 3783, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3759, 3760, 3762, or 3783, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3759, 3760, 3762, or 3783. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5' or 3'

end when paired with a sense strand). The antisense strand may include a GalNAc moiety connected at one of the ends (e.g. 5' end or 3' end).

[0060] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3759. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3759, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3759, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3759. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5 or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0061] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3760. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3760, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3760, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3760. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5 or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0062] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3762. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3762, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3762, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3762. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5 or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

[0063] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3783. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3783, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3783, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3783. The antisense strand may include any internucleoside linkages or nucleoside modifications described herein. The antisense strand may include an overhang (e.g. 2 bases on a 5 or 3' end when paired with a sense strand). The sense strand may include a GalNAc moiety connected at one of the ends.

B. ASOs

[0064] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. In some embodiments, the ASO is 14-30 nucleosides in length. In some embodiments, the ASO is at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. In some embodiments, the ASO is 15-25 nucleosides in length. In some embodiments, the ASO is 20 nucleosides in length.

[0065] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and comprising a nucleoside sequence complementary to about 12-30 contiguous nucleosides of a full-length human FGG mRNA sequence such as SEQ ID NO: 3621; wherein (i) the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier. In some embodiments, the ASO comprise a nucleoside sequence complementary to at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of SEQ ID NO: 3621.

C. Modification patterns

[0066] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier. In some embodiments, the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. A phosphorothioate may include a nonbridging oxygen atom in a phosphate backbone of the oligonucleotide that is replaced by sulfur. Modified internucleoside linkages may be included in siRNAs or ASOs. Benefits of the modified internucleoside linkage may include decreased toxicity or improved pharmacokinetics.

[0067] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a modified internucleoside linkage, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 18 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises no more than 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises 2 or more modified internucleoside linkages, 3 or more modified internucleoside linkages, 4 or more modified internucleoside

linkages, 5 or more modified internucleoside linkages, 6 or more modified internucleoside linkages, 7 or more modified internucleoside linkages, 8 or more modified internucleoside linkages, 9 or more modified internucleoside linkages, 10 or more modified internucleoside linkages, 11 or more modified internucleoside linkages, 12 or more modified internucleoside linkages, 13 or more modified internucleoside linkages, 14 or more modified internucleoside linkages, 15 or more modified internucleoside linkages, 16 or more modified internucleoside linkages, 17 or more modified internucleoside linkages, 18 or more modified internucleoside linkages, 19 or more modified internucleoside linkages, or 20 or more modified internucleoside linkages.

[0068] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises the modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises HLA. In some embodiments, the modified nucleoside comprises CeNA. In some embodiments, the modified nucleoside comprises a 2'-methoxyethyl group. In some embodiments, the modified nucleoside comprises a 2'-O-alkyl group. In some embodiments, the modified nucleoside comprises a 2'-O-allyl group. In some embodiments, the modified nucleoside comprises a 2'-fluoro group. In some embodiments, the modified nucleoside comprises a 2'-deoxy group. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside. In some embodiments, the modified nucleoside comprises a 2'-deoxyfluoro nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-NMA nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-DMAEOE nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-aminopropyl (2'-O-AP) nucleoside. In some embodiments, the modified nucleoside comprises 2'-ara-F. In some embodiments, the modified nucleoside comprises one or more 2'fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. Benefits of the modified nucleoside may include decreased toxicity or improved pharmacokinetics.

[0069] In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 modified nucleosides, or a range of nucleosides defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 19 modified nucleosides. In some embodiments, the oligonucleotide comprises no more than 21 modified nucleosides. In some embodiments, the oligonucleotide comprises 2 or more modified nucleosides, 3 or more modified nucleosides, 4 or more modified nucleosides, 5 or more modified nucleosides, 6 or more modified nucleosides, 7 or more modified nucleosides, 8 or more modified nucleosides, 9 or more modified nucleosides, 10 or more modified nucleosides, 11 or more modified nucleosides, 12 or more modified

nucleosides, 13 or more modified nucleosides, 14 or more modified nucleosides, 15 or more modified nucleosides, 16 or more modified nucleosides, 17 or more modified nucleosides, 18 or more modified nucleosides, 19 or more modified nucleosides, 20 or more modified nucleosides, or 21 or more modified nucleosides.

[0070] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a moiety attached at a 3' or 5' terminus of the oligonucleotide. Examples of moieties include a hydrophobic moiety or a sugar moiety, or a combination thereof. In some embodiments, the oligonucleotide is an siRNA having a sense strand, and the moiety is attached to a 5' end of the sense strand. In some embodiments, the oligonucleotide is an siRNA having a sense strand, and the moiety is attached to a 3' end of the sense strand. In some embodiments, the oligonucleotide is an siRNA having an antisense strand, and the moiety is attached to a 5' end of the antisense strand. In some embodiments, the oligonucleotide is an siRNA having an antisense strand, and the moiety is attached to a 3' end of the antisense strand. In some embodiments, the oligonucleotide is an ASO, and the moiety is attached to a 5' end of the ASO. In some embodiments, the oligonucleotide is an ASO, and the moiety is attached to a 3' end of the ASO.

[0071] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a hydrophobic moiety. The hydrophobic moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The hydrophobic moiety may include a lipid such as a fatty acid. The hydrophobic moiety may include a hydrocarbon. The hydrocarbon may be linear. The hydrocarbon may be non-linear. The hydrophobic moiety may include a lipid moiety or a cholesterol moiety, or a combination thereof.

[0072] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α -tocopherol, or a combination thereof.

[0073] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a sugar moiety. The sugar moiety may include an N-acetyl galactose moiety (e.g. a N-acetylgalactosamine (GalNAc) moiety), an N-acetyl glucose moiety (e.g. an N-acetylglucosamine (GlcNAc) moiety), a fucose moiety, or a mannose moiety. The sugar moiety may include 1, 2, 3, or more sugar molecules. The sugar moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The sugar moiety may include an N-acetyl galactose moiety. The sugar moiety may include an N-acetylgalactosamine (GalNAc) moiety. The sugar moiety may include an N-acetyl glucose moiety. The sugar moiety may include N-acetylglucosamine (GlcNAc) moiety. The sugar moiety may include a fucose moiety. The sugar moiety may include a mannose moiety. N-acetyl glucose, GlcNAc, fucose, or mannose may be useful for targeting macrophages since they may target or bind a mannose receptor such as CD206.

[0074] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) moiety. GalNAc may be useful for hepatocyte targeting, neural (e.g., CNS (e.g., brain), or CSF targeting. The GalNAc moiety may include 1, 2, 3, or more GalNAc molecules. The GalNAc moiety may be attached at a 3' or 5' terminus of the oligonucleotide.

[0075] Non-limiting examples of GalNAc ligands are shown in FIG. 1 and FIG. 2. In some embodiments, the oligonucleotide is conjugated to the GalNAc ligand in FIG. 1. In the GalNAc ligand shown in FIG. 1, J indicates a point of attachment to an oligonucleotide. In some embodiments, J is at a 5' end of the oligonucleotide. In some embodiments, J is at a 3' end of the oligonucleotide. In the GalNAc ligand shown in FIG. 1, n may be any number. For example, n may be 1-10. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or a range defined by any two of the aforementioned integers. In some embodiments, n is 2. In embodiments in which n is 2 and the oligonucleotide is connected at J, the GalNAc moiety may be referred to as "GalNAc#1" or "GalNAc1."

[0076] In some embodiments, the oligonucleotide is conjugated to the GalNAc ligand in FIG. 2. The wavy line in FIG. 1 indicates a point of attachment to an oligonucleotide. In some embodiments, the wavy line is at a 5' end of the oligonucleotide. In some embodiments, the wavy line is at a 3' end of the oligonucleotide. In embodiments in which the oligonucleotide is connected at the wavy line, the GalNAc moiety may be referred to as "GalNAc#23" or "GalNAc23."

[0077] The oligonucleotide may include purines. Examples of purines include adenine (A) or guanine (G), or modified versions thereof. The oligonucleotide may include pyrimidines. Examples of pyrimidines include cytosine (C), thymine (T), or uracil (U), or modified versions thereof.

[0078] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. 2'-O-methyl may include 2' O-methyl. Where 2'-O-methyl modifications are described, it is contemplated that a 2'-methyl modification may be included, and vice versa.

[0079] In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[0080] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified

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

[0081] In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines, and all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines, and all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines, and all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines, and all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and all purines of the oligonucleotide comprise 2' fluoro modified purines.

[0082] In some cases, the oligonucleotide comprises a particular modification pattern. In some embodiments, position 9 counting from the 5' end of the of a strand of the oligonucleotide may have a 2'F modification. In some embodiments, when position 9 of a strand of the oligonucleotide is a pyrimidine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense strand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions

5 and 11 of a strand of the oligonucleotide are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[0083] In some embodiments, when position 9 of a strand of the oligonucleotide is a purine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense strand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are purines, then both of these purines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[0084] In some cases, position 9 of a strand of the oligonucleotide can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of a strand of the oligonucleotide. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to these a strand of the oligonucleotide rules.

[0085] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2' fluoro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine; all purines of the sense strand comprises 2'-O-methyl modified purines; 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2' fluoro-modified

pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides.

[0086] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2' fluoro-modified purine, provided there are not three 2' fluoro-modified purine in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine; all pyrimidine of the sense strand comprises 2'-O-methyl modified pyrimidines; 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2' fluoro-modified purines, provided there are not three 2' fluoro-modified purines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, there are not three 2' fluoro-modified purines in a row. In some embodiments, there are not three 2' fluoro-modified pyrimidines in a row.

[0087] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2' fluoro-modified nucleotides. In some embodiments, all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2' fluoro-modified purines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2' fluoro-modified nucleotides; all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2' fluoro-modified purines; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2' fluoro-modified nucleotides and unmodified deoxyribonucleotides.

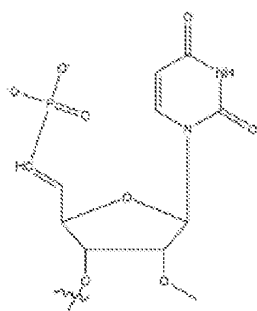
[0088] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2' fluoro-

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

[0089] In some embodiments, the moiety includes a negatively charged group attached at a 5' end of the oligonucleotide. This may be referred to as a 5'-end group. In some embodiments, the negatively charged group is attached at a 5' end of an antisense strand of an siRNA disclosed herein. The 5'-end group may be or include a 5'-end phosphorothioate, 5'-end phosphorodithioate, 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate, 5'-end cyclopropyl phosphonate, or a 5'-deoxy-5'-C-malonyl. The 5'-end group may comprise 5'-VP. In some embodiments, the 5'-VP comprises a trans-vinylphosphate or cis-vinylphosphate. The 5'-end group may include an extra 5' phosphate. A combination of 5'-end groups may be used.

[0090] In some embodiments, the oligonucleotide includes a negatively charged group. The negatively charged group may aid in cell or tissue penetration. The negatively charged group may be attached at a 5' or 3' end (e.g. a 5' end) of the oligonucleotide. This may be referred to as an end group. The end group may be or include a phosphorothioate, phosphorodithioate, vinylphosphonate, methylphosphonate, cyclopropyl phosphonate, or a deoxy-C-malonyl. The end group may include an extra 5' phosphate such as an extra 5' phosphate. A combination of end groups may be used.

[0091] In some embodiments, the oligonucleotide includes a phosphate mimic. In some embodiments, the phosphate mimic comprises vinyl phosphonate. In some embodiments, the vinyl phosphonate comprises a trans-vinylphosphate. In some embodiments, the vinyl phosphonate comprises a cis-vinylphosphate. An example of a nucleotide that includes a vinyl phosphonate is shown below.



5' vinylphosphonate 2' O Methyl Uridine

[0092] In some embodiments, the vinyl phosphonate increases the stability of the oligonucleotide. In some embodiments, the vinyl phosphonate increases the accumulation of the oligonucleotide in tissues. In some embodiments, the vinyl phosphonate protects the oligonucleotide from an exonuclease or a phosphatase. In some embodiments, the vinyl phosphonate improves the binding affinity of the oligonucleotide with the siRNA processing machinery.

[0093] In some embodiments, the oligonucleotide includes 1 vinyl phosphonate. In some embodiments, the oligonucleotide includes 2 vinyl phosphonates. In some embodiments, the oligonucleotide includes 3 vinyl phosphonates. In some embodiments, the oligonucleotide includes 4 vinyl phosphonates. In some embodiments, the antisense strand of the oligonucleotide comprises a vinyl phosphonate at the 5' end. In some embodiments, the antisense strand of the oligonucleotide comprises a vinyl phosphonate at the 3' end. In some embodiments, the sense strand of the oligonucleotide comprises a vinyl phosphonate at the 5' end. In some embodiments, the sense strand of the oligonucleotide comprises a vinyl phosphonate at the 3' end.

1. Hydrophobic moieties

[0094] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a hydrophobic moiety. The hydrophobic moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The hydrophobic moiety may include a lipid such as a fatty acid. The hydrophobic moiety may include a hydrocarbon. The hydrocarbon may be linear. The hydrocarbon may be non-linear. The hydrophobic moiety may include a lipid moiety or a cholesterol moiety, or a combination thereof.

[0095] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosaheptaenoyl, myristyl, palmityl, stearyl, or α -tocopherol, or a combination thereof.

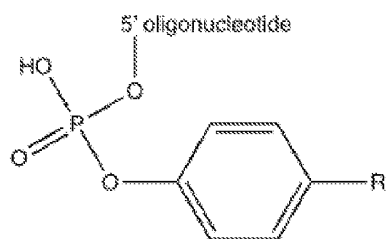
[0096] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a hydrophobic ligand or moiety. In some embodiments, the hydrophobic ligand or moiety comprises cholesterol. In some embodiments, the hydrophobic ligand or moiety comprises a cholesterol derivative. In some embodiments, the hydrophobic ligand or moiety is attached at a 3' terminus of the oligonucleotide. In some embodiments, the

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

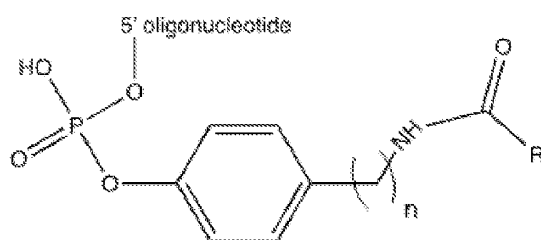
[0097] In some embodiments, a hydrophobic moiety is attached to the oligonucleotide (e.g. a sense strand and/or an antisense strand of a siRNA). In some embodiments, a hydrophobic moiety is attached at a 3' terminus of the oligonucleotide. In some embodiments, a hydrophobic moiety is attached at a 5' terminus of the oligonucleotide. In some embodiments, the hydrophobic moiety comprises cholesterol. In some embodiments, the hydrophobic moiety includes a cyclohexanyl.

[0098] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, a lipid is attached at a 3' terminus of the oligonucleotide. In some embodiments, a lipid is attached at a 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanyl, docosahexaenoyl, myristyl, palmityl, stearyl, or α -tocopherol, or a combination thereof. In some embodiments, the lipid comprises stearyl, lithocholoyl, docosanyl, docosahexaenyl, or myristyl. In some embodiments, the lipid comprises cholesterol. In some embodiments, the lipid includes a sterol such as cholesterol. In some embodiments, the lipid comprises stearyl, t-butylphenol, n-butylphenol, octylphenol, dodecylphenol, phenyl n-dodecyl, octadecylbenzamide, hexadecylbenzamide, or octadecylcyclohexyl. In some embodiments, the lipid comprises phenyl para C12.

[0099] In some embodiments, the oligonucleotide comprises any aspect of the following structure:



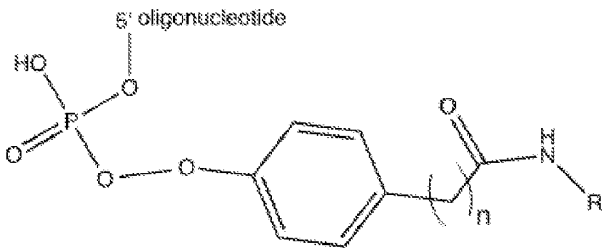
. In some embodiments, the oligonucleotide comprises any aspect



of the following structure:

. In some embodiments,

the oligonucleotide comprises any aspect of the following structure:



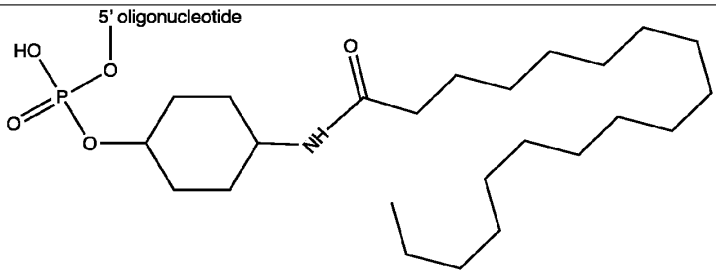
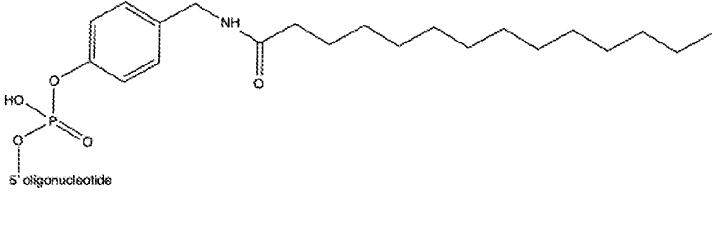
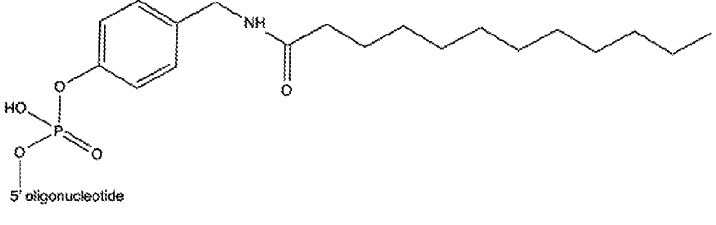
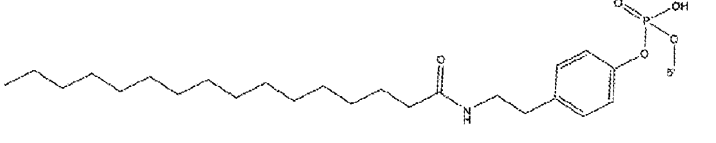
. In some embodiments, the oligonucleotide comprises any aspect of the following structure: The aspect included in the oligonucleotide may include the entire structure, or may include the lipid moiety, of any of the structures shown. In some embodiments, n is 1-3. In some embodiments, n is 1. In some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

[00100] In some embodiments, the lipid includes a fatty acid. In some embodiments, the lipid comprises a lipid depicted in Table 1. The example lipid moieties in Table 1 are shown attached at a 5' end of an oligonucleotide, in which the 5' terminal phosphate of the oligonucleotide is shown with the lipid moiety. In some embodiments, a lipid moiety in Table 1 may be attached at a different point of attachment than shown. For example, the point of attachment of any of the lipid moieties in the table may be at a 3' oligonucleotide end. In some embodiments, the lipid is used for targeting the oligonucleotide to a non-hepatic cell or tissue.

(1) Table 1: Hydrophobic moiety examples

Hydrophobic Moiety Description	Hydrophobic Moiety Name	Example Conjugation
stearyl	ETL3	
t-butylphenyl	ETL7	

n-butylphenyl	ETL8	
octylphenyl	ETL9	
dodecylphenyl	ETL10	
phenyl n-dodecyl	ETL12	
octadecylbenzamide	ETL13	
hexadecylbenzamide	ETL15	

octadecylcyclohexyl	ETL16	
myristamido methylphenyl	ETL18	
lauramido methylphenyl	ETL19	
phenethyl-palmityl	ETL20	

[00101] In some embodiments, the lipid or lipid moiety includes 16 to 18 carbons. In some embodiments, the lipid includes 16 carbons. In some embodiments, the lipid includes 17 carbons. In some embodiments, the lipid includes 18 carbons. In some embodiments, the lipid moiety includes 16 carbons. In some embodiments, the lipid moiety includes 17 carbons. In some embodiments, the lipid moiety includes 18 carbons.

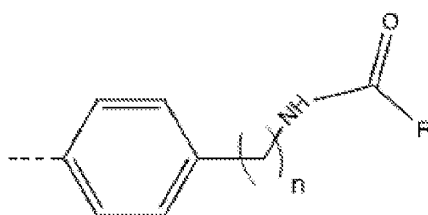
[00102] The hydrophobic moiety may include a linker that comprises a carbocycle. The carbocycle may be six-membered. Some examples of a carbocycle include phenyl or cyclohexyl. The linker may include a phenyl. The linker may include a cyclohexyl. The lipid may be attached to the carbocycle, which may in turn be attached at a phosphate (e.g. 5' or 3' phosphate) of the oligonucleotide. In some embodiments, the lipid or hydrocarbon, and the end of the sense are connected to the phenyl or cyclohexyl linker in the 1,4; 1,3; or 1,2 substitution pattern (e.g. the para, meta, or ortho phenyl configuration). In some embodiments, the lipid or hydrocarbon, and the end of the sense are connected to the phenyl or cyclohexyl linker in the 1,4 substitution pattern (e.g. the para phenyl configuration). The lipid may be attached to the carbocycle in the 1,4 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the 1,3 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the 1,2 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the ortho orientation relative to the oligonucleotide. The lipid may be

attached to the carbocycle in the para orientation relative to the oligonucleotide. The lipid may be attached to the carbocycle in the meta orientation relative to the oligonucleotide.

[00103] The lipid moiety may comprise or consist of the following structure

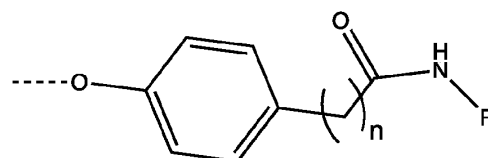


. In some embodiments, the lipid moiety comprises or



consists of the following structure:

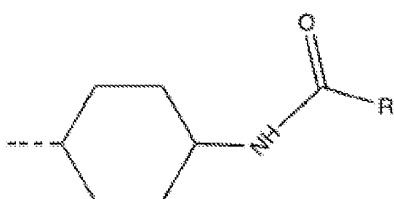
. In some embodiments,



the lipid moiety comprises the following structure:

. In

some embodiments, the lipid moiety comprises or consist of the following structure:



. In some embodiments, the dotted line indicates a covalent

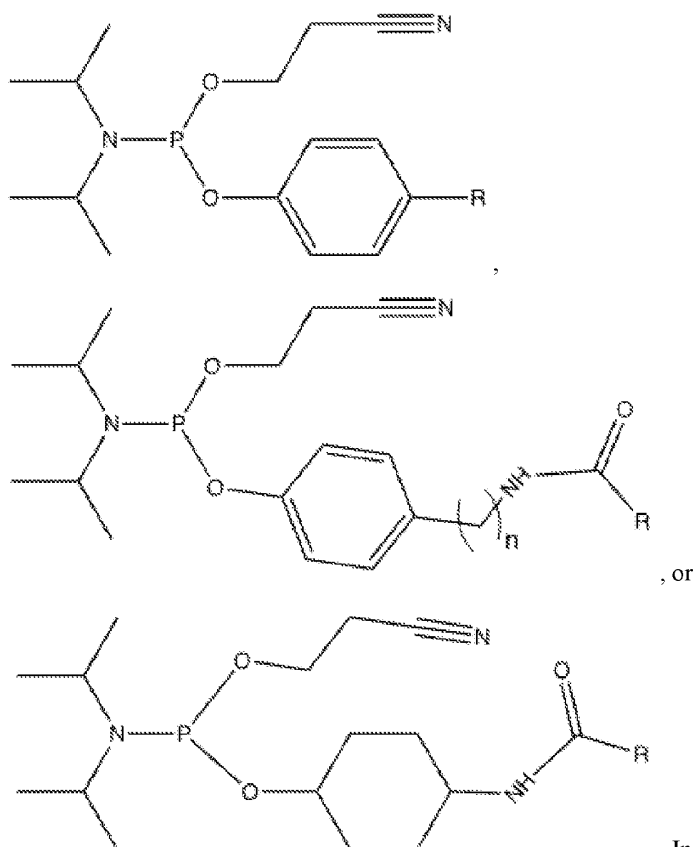
connection. The covalent connection may be between an end of the sense or antisense strand. For example, the connection may be to the 5' end of the sense strand. In some embodiments, n is 0-3. In some embodiments, n is 1-3. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments,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

[00104] The lipid moiety may be attached at a 5' end of the oligonucleotide. The 5' end may have one phosphate linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have two phosphates linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have three phosphates linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have one phosphate connected to the 5' carbon of a sugar of the oligonucleotide, where the one phosphate is connected to the lipid moiety. The 5' end may have two phosphates connected to the 5' carbon of a sugar of the oligonucleotide, where the one of the two phosphates is connected to the lipid

moiety. The 5' end may have three phosphates connected to the 5' carbon of a sugar of the oligonucleotide, where the one of the three phosphates is connected to the lipid moiety. The sugar may include a ribose. The sugar may include a deoxyribose. The sugar may be modified such as a 2' modified sugar (e.g. a 2' O-methyl or 2' fluoro ribose). A phosphate of the 5' end may include a modification such as a sulfur in place of an oxygen. Two phosphates of the 5' end may include a modification such as a sulfur in place of an oxygen. Three phosphates of the 5' end may include a modification such as a sulfur in place of an oxygen.

[00105] In some embodiments, the oligonucleotide includes 1 lipid moiety. In some embodiments, the oligonucleotide includes 2 lipid moieties. In some embodiments, the oligonucleotide includes 3 lipid moieties. In some embodiments, the oligonucleotide includes 4 lipid moieties.

[00106] Some embodiments relate to a method of making an oligonucleotide comprising a hydrophobic conjugate. A strategy for making hydrophobic conjugates may include use of a phosphoramidite reagent based upon a 6-membered ring alcohol such as a phenol or cyclohexanol. The phosphoramidite may be reacted to a nucleotide to connect the nucleotide to the hydrophobic moiety, and thereby produce the hydrophobic conjugate. Some examples of phosphoramidite reagents that may be used to produce a hydrophobic conjugate are provided as follows:



. In some embodiments, n is 1-3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9,

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, R comprises or consists of an alkyl group containing 4-18 carbons. Any one of the phosphoramidite reagents may be reacted to a 5' end of an oligonucleotide to produce an oligonucleotide comprising a hydrophobic moiety. In some embodiments, the phosphoramidite reagents is reacted to a 5' end of a sense strand of an siRNA. The sense strand may then be hybridized to an antisense strand to form a duplex. The hybridization may be performed by incubating the sense and antisense strands in solution at a given temperature. The temperature may be gradually reduced. The temperature may comprise or include a temperature comprising an annealing temperature for the sense and antisense strands. The temperature may be below or include a temperature below the annealing temperature for the sense and antisense strands. The temperature may be below a melting temperature of the sense and antisense strands.

[00107] The lipid may be attached to the oligonucleotide by a linker. The linker may include a polyethyleneglycol (e.g. tetraethyleneglycol).

[00108] The modifications described herein may be useful for delivery to a cell or tissue, for example, extrahepatic delivery or targeting of an oligonucleotide composition. The modifications described herein may be useful for targeting an oligonucleotide composition to a cell or tissue.

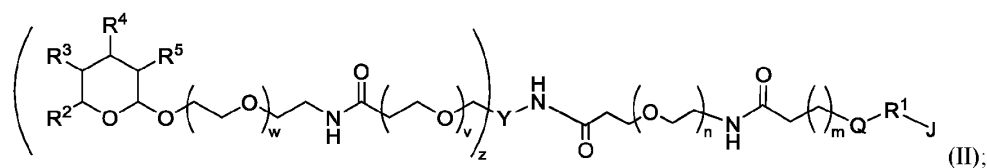
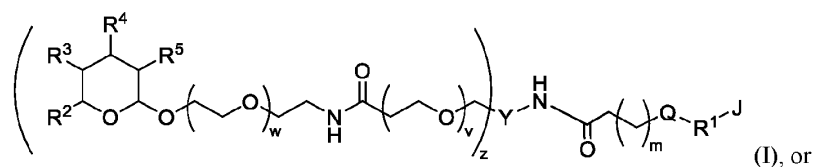
2. Sugar moieties

[00109] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a sugar moiety. The sugar moiety may include an N-acetyl galactose moiety (e.g. an N-acetylgalactosamine (GalNAc) moiety), an N-acetyl glucose moiety (e.g. an N-acetylglucosamine (GlcNAc) moiety), a fucose moiety, or a mannose moiety. The sugar moiety may include 1, 2, 3, or more sugar molecules. The sugar moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The sugar moiety may include an N-acetyl galactose moiety. The sugar moiety may include an N-acetylgalactosamine (GalNAc) moiety. The sugar moiety may include an N-acetyl glucose moiety. The sugar moiety may include N-acetylglucosamine (GlcNAc) moiety. The sugar moiety may include a fucose moiety. The sugar moiety may include a mannose moiety. N-acetyl glucose, GlcNAc, fucose, or mannose may be useful for targeting macrophages when they target or bind a mannose receptor such as CD206. The sugar moiety may be useful for binding or targeting an asialoglycoprotein receptor such as an asialoglycoprotein receptor of a hepatocyte. The GalNAc moiety may bind to an asialoglycoprotein receptor. The GalNAc moiety may target a hepatocyte.

[00110] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) moiety. GalNAc may be useful for hepatocyte targeting. The GalNAc moiety may include a bivalent or trivalent branched linker. The oligo may be attached to 1, 2 or 3 GalNAcs through a bivalent or trivalent branched linker. The GalNAc moiety may include 1, 2, 3, or more GalNAc molecules. The GalNAc moiety may be attached at a 3' or 5' terminus of the oligonucleotide.

[00111] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) ligand for hepatocyte targeting. In some embodiments, the composition comprises GalNAc. In some embodiments, the composition comprises a GalNAc derivative. In some embodiments, the GalNAc ligand is attached at a 3' terminus of the oligonucleotide. In some embodiments, the GalNAc ligand is attached at a 5' terminus of the oligonucleotide. In some embodiments, the composition comprises a sense strand, and the GalNAc ligand is attached to the sense strand (e.g. attached to a 5' end of the sense strand, or attached to a 3' end of the sense strand). In some embodiments, the composition comprises an antisense strand, and the GalNAc ligand is attached to the antisense strand (e.g. attached to a 5' end of the antisense strand, or attached to a 3' end of the antisense strand). In some embodiments, the composition comprises a GalNAc ligand attached at a 3' or 5' terminus of the oligonucleotide.

[00112] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises a GalNAc moiety. The GalNAc moiety may be included in any formula, structure, or GalNAc moiety shown below. In some embodiments, described herein is a compound (e.g. oligonucleotide) represented by Formula (I) or (II):



or a salt thereof, wherein

J is an oligonucleotide;

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

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

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

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

if z is 3, Y is C

if z is 2, Y is CR⁶, or

if z is 1, Y is C(R⁶)₂;

Q is selected from:

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

alkyl, wherein the C₁₋₆ alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, and -NH₂;

R¹ is a linker selected from:

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

each R² is independently selected from:

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

R³ and R⁴ are each independently selected from:

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

each R⁵ is independently selected from:

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

each R⁶ is independently selected from:

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

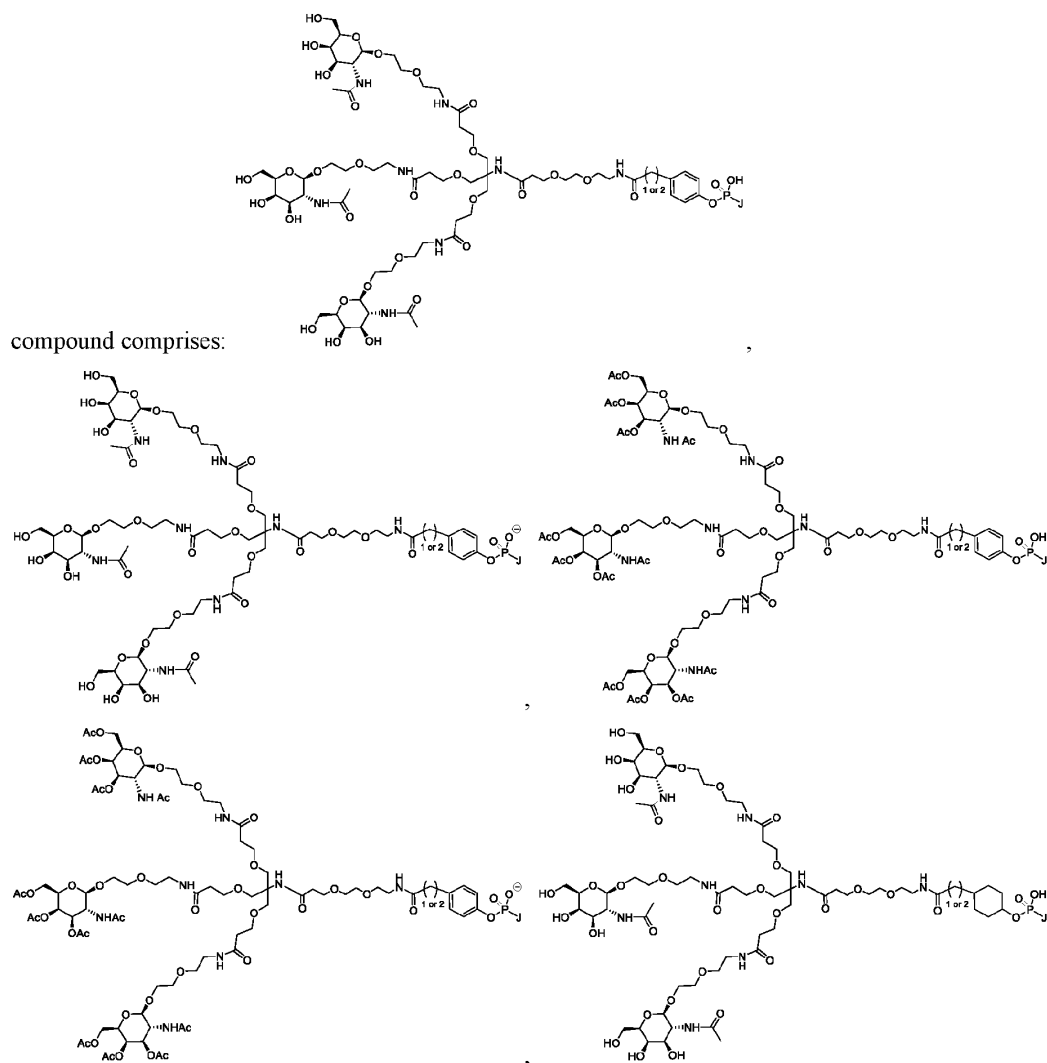
each R⁷ is independently selected from:

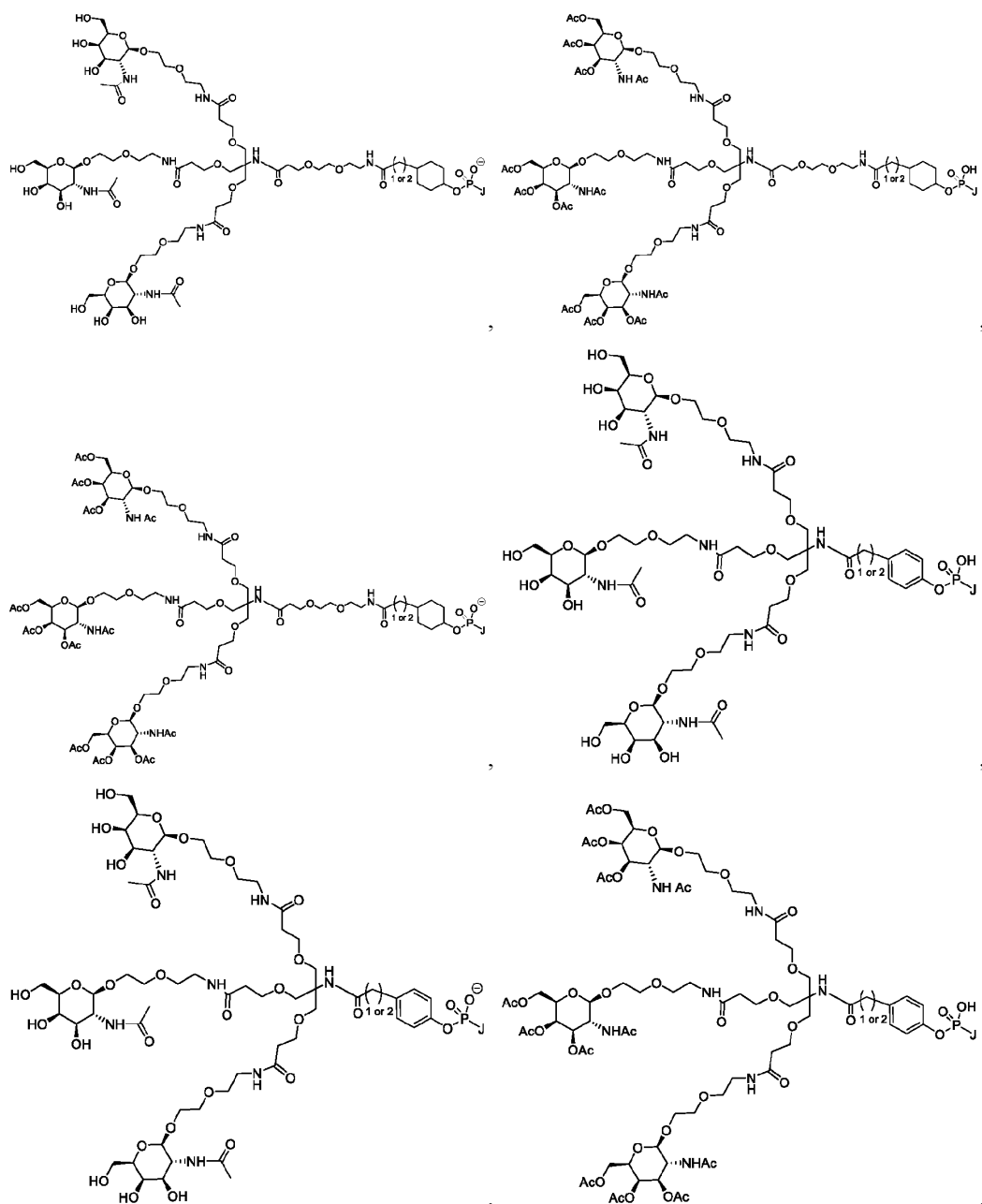
hydrogen;
C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO₂, -NH₂, =O, =S, -O-C₁₋₆ alkyl, -S-C₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle;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

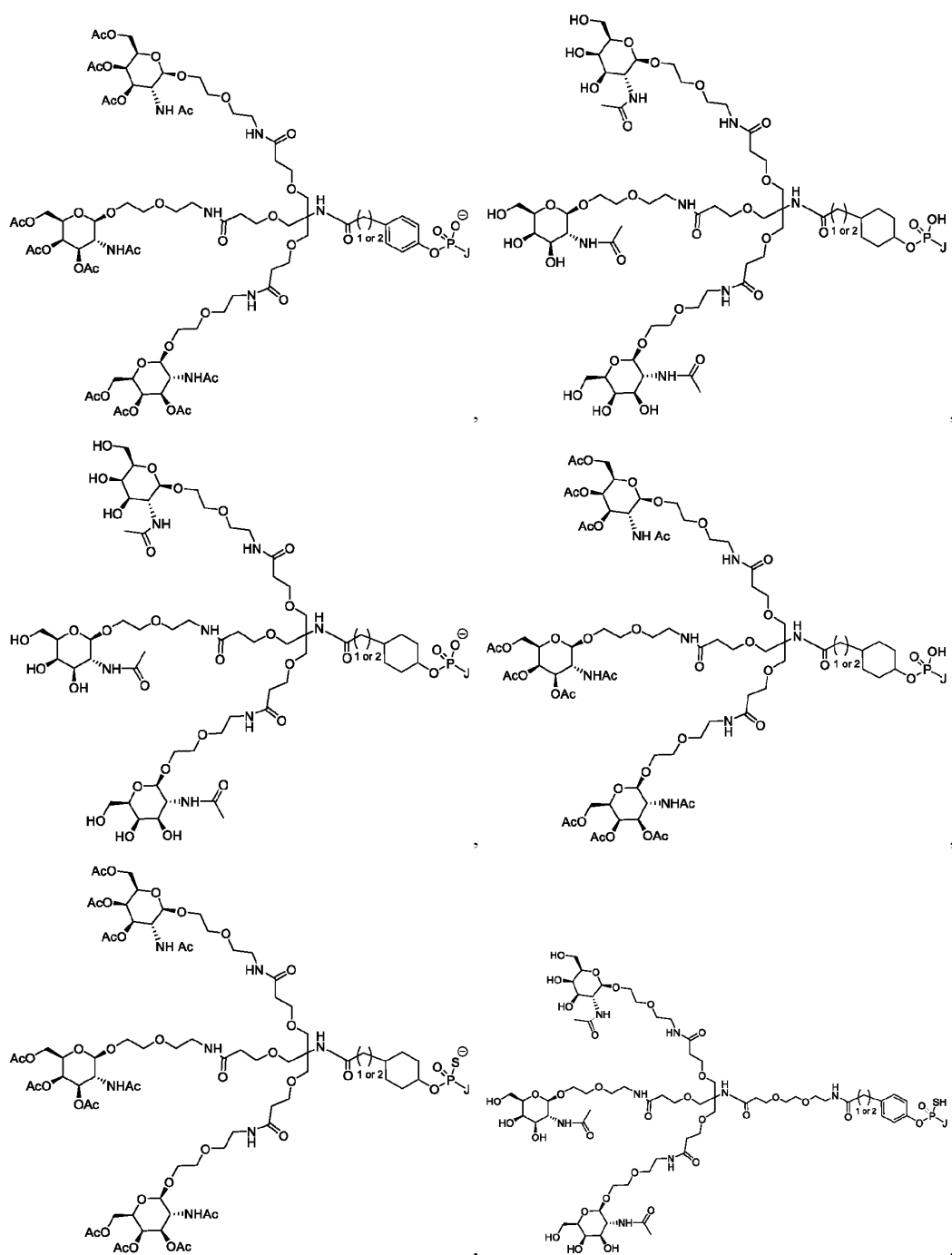
[00113] In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is 1. In some embodiments, each v is independently selected from any value from 1 to 10. In some

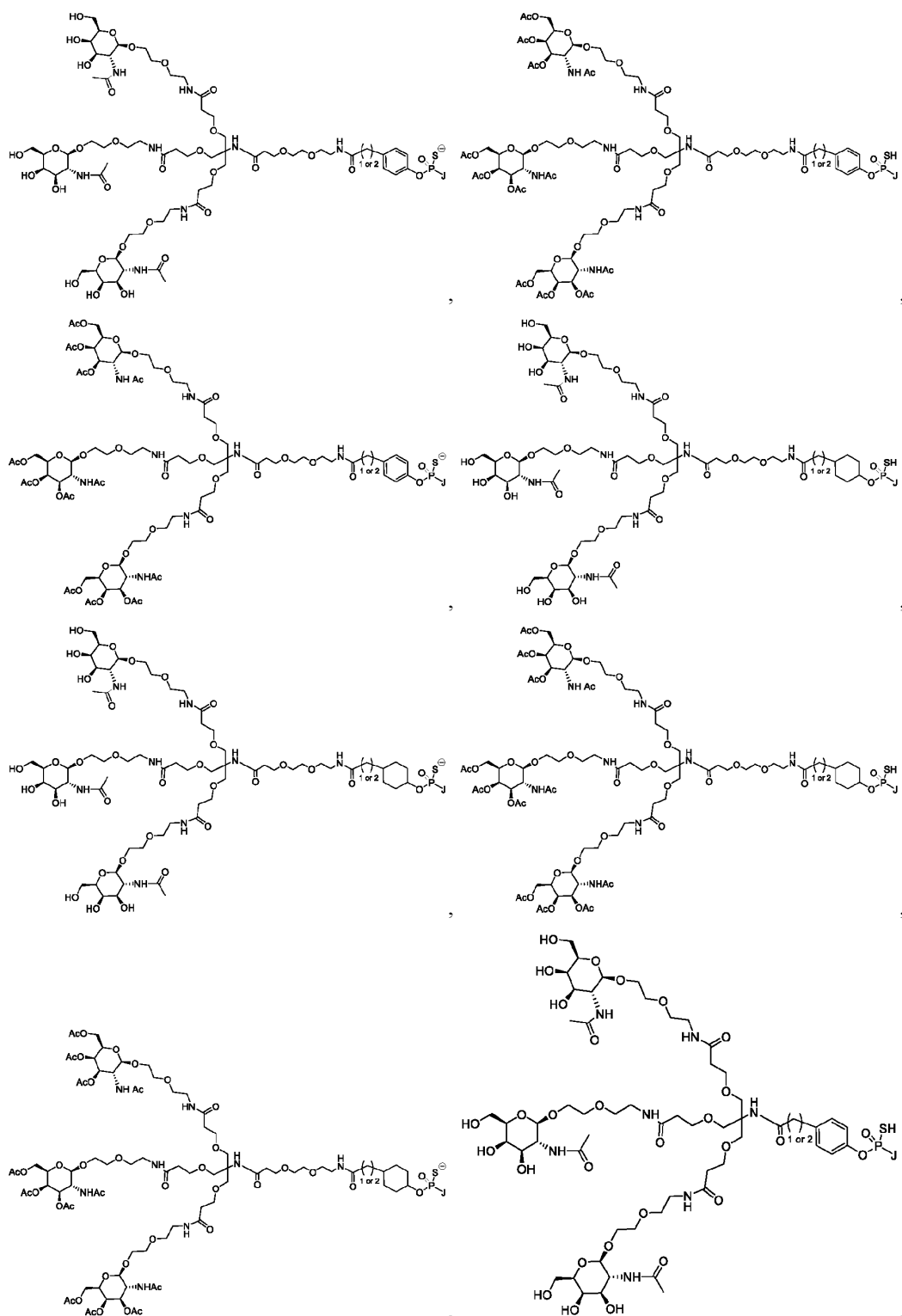
embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is 1. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is 2. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from 1 and 2. In some embodiments, z is 3 and Y is C. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl. In some embodiments, Q is selected from cyclohexyl. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O)O-$, $-SP(O)(O)O-$, $-OP(S)(O)O-$, $-OP(O)(S)O-$, $-OP(O)(O)S-$, $-OP(O)(OR^7)NR^7$, $-OP(O)(N(R^7)_2)NR^7$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)$, and $-OPN(R^7)_2$. NR^7 . In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O)O-$, $-SP(O)(O)O-$, $-OP(S)(O)O-$, $-OP(O)(S)O-$, $-OP(O)(O)S-$, and $-OP(OR^7)O-$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O)O-$, $-OP(S)(O)O-$, $-OP(O)(S)O-$, and $-OP(OR^7)O-$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$ and $-OP(OR^7)O-$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, $-OR^7$, $-OC(O)R^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, and $-S(O)R^7$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^3 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^3 is selected from $-OR^7$, $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^3 is selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^4 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^4 is selected from $-OR^7$, $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^4 is selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$. In some embodiments, each R^7 is independently selected from: hydrogen; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, or 3- to 10-membered heterocycle. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl) $_2$, and $-NH(C_{1-6}$ alkyl). In some embodiments,

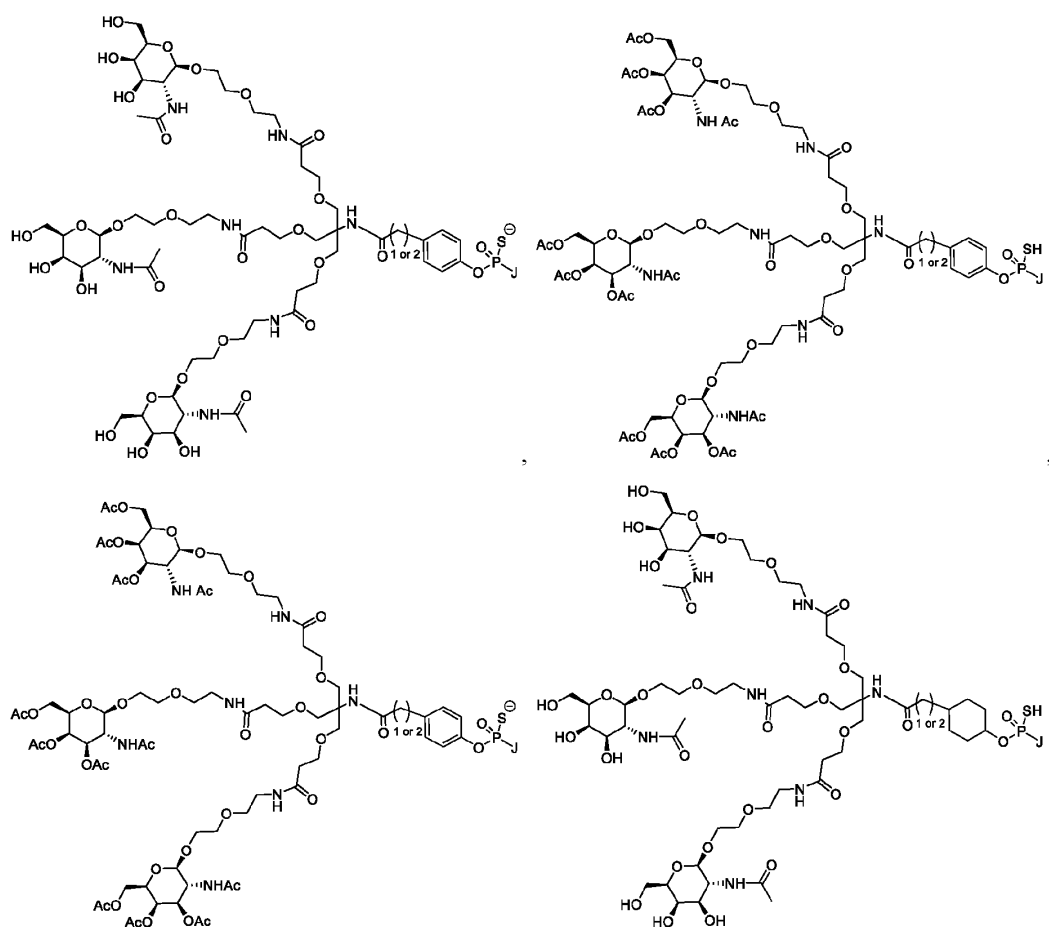
each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, and $-SH$. In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C ; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, and $-OP(OR^7)O-$; R^2 is C_1 alkyl substituted with $-OH$ or $-OC(O)CH_3$; R^3 is $-OH$ or $-OC(O)CH_3$; R^4 is $-OH$ or $-OC(O)CH_3$; and R^5 is $-NH(O)CH_3$. In some embodiments, the

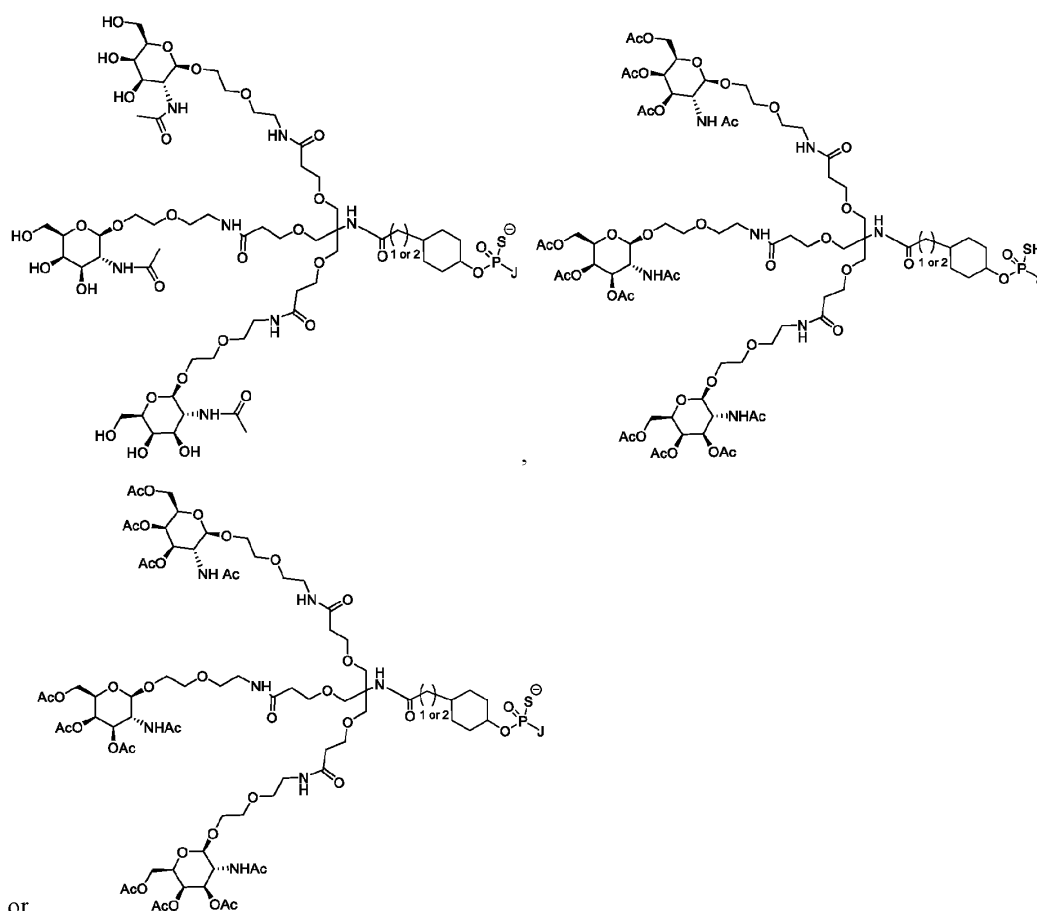






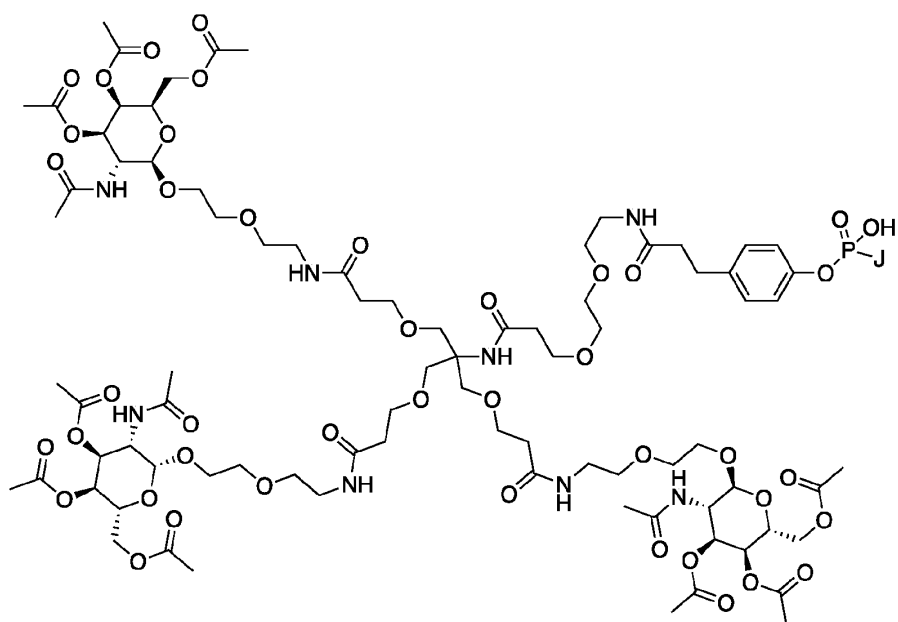






[00114] In some embodiments, the oligonucleotide (J) is attached at a 5' end or a 3' end of the oligonucleotide. In some embodiments, the oligonucleotide comprises DNA. In some embodiments, the oligonucleotide comprises RNA. In some embodiments, the oligonucleotide comprises one or more modified internucleoside linkages. In some embodiments, the one or more modified internucleoside linkages comprise alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages. In some embodiments, the compound binds to an asialoglycoprotein receptor. In some embodiments, the compound targets a hepatocyte.

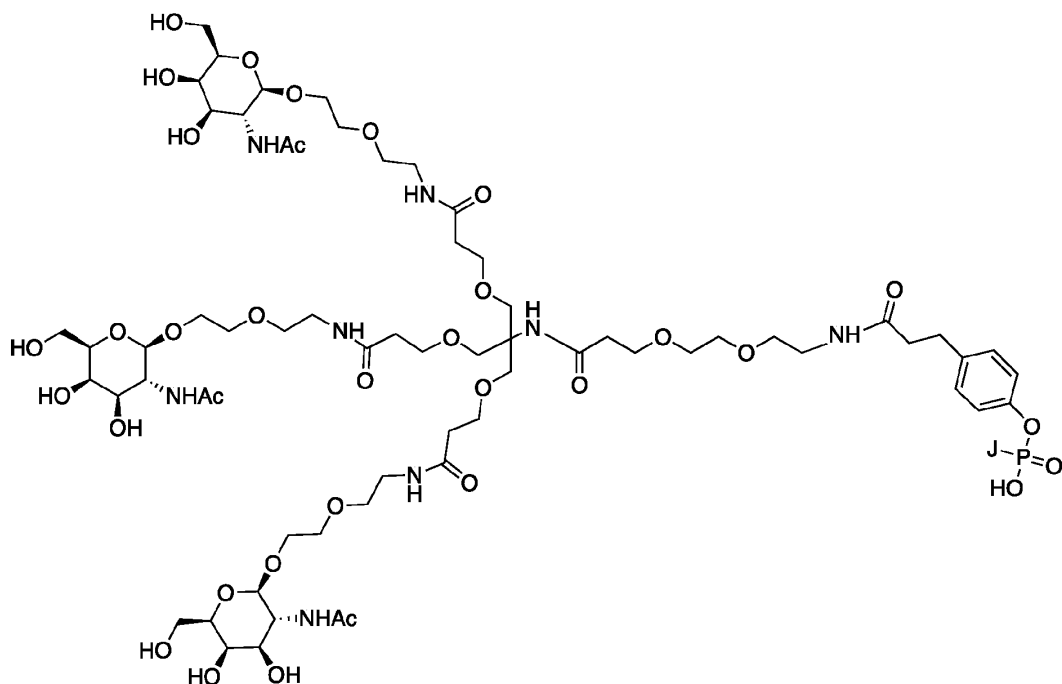
[00115] Some embodiments include the following, where J is the oligonucleotide:



. J may

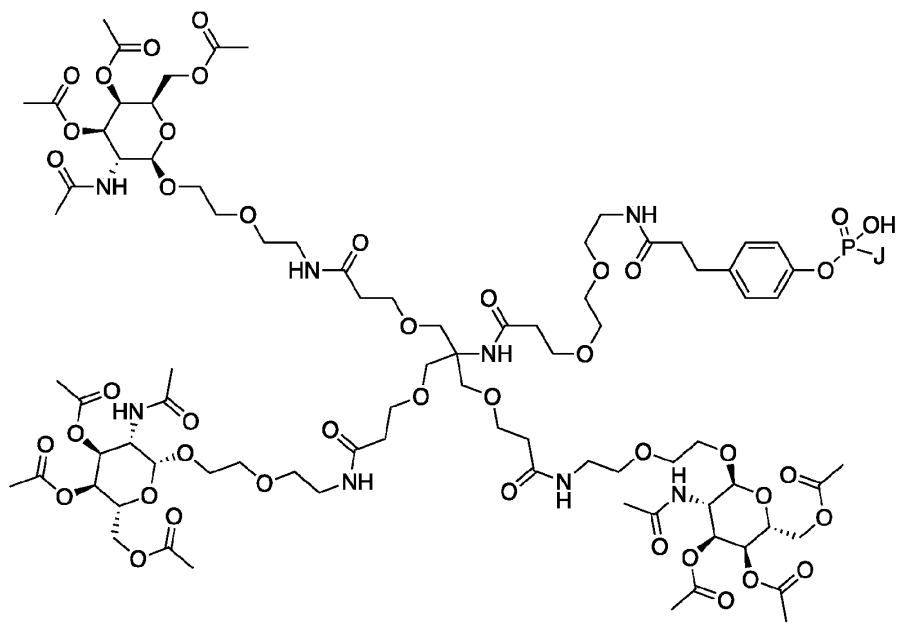
include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[00116] Some embodiments include the following, where J is the oligonucleotide:



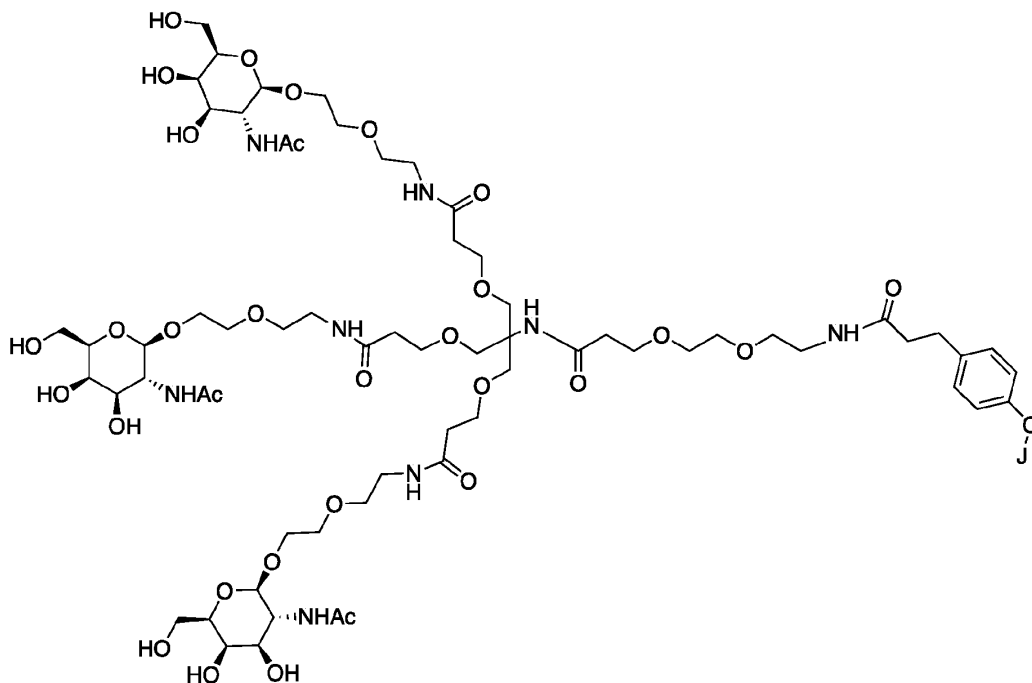
J may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[00117] Some embodiments include the following, where J is the oligonucleotide:



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

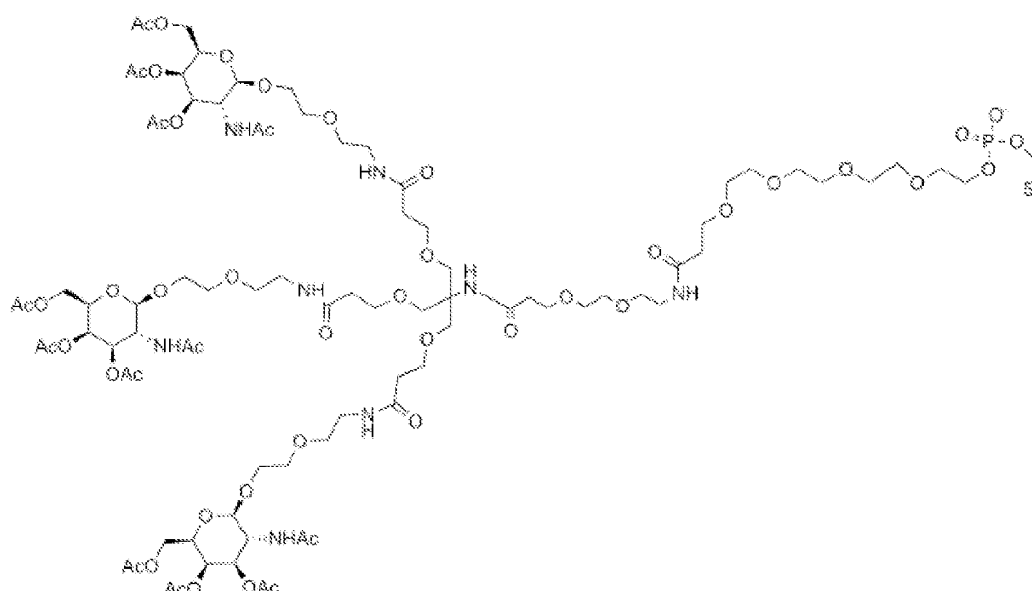
[00118] Some embodiments include the following, where J is the oligonucleotide:



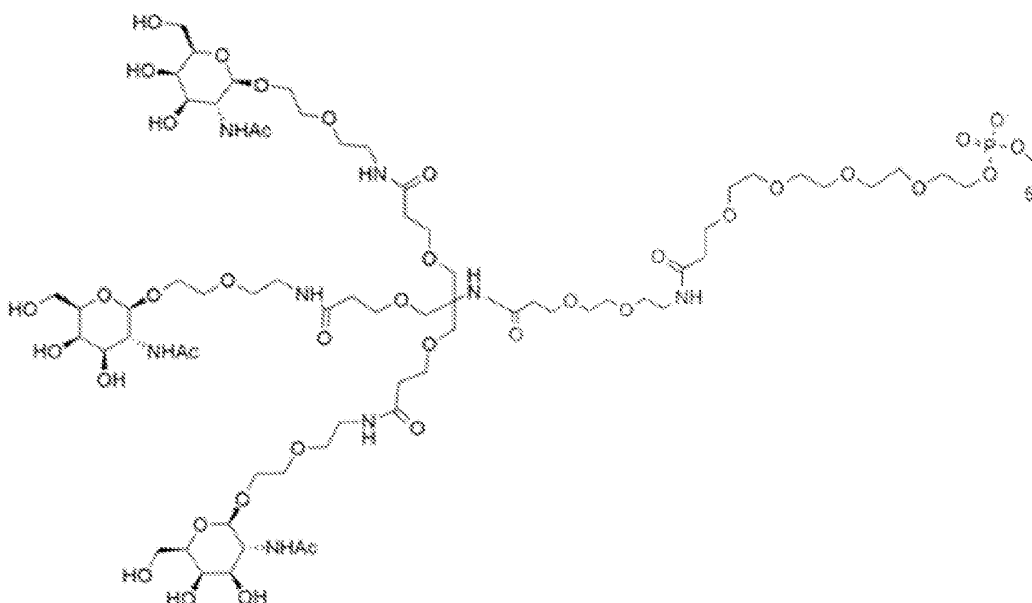
The structure in this compound attached to the oligonucleotide (J) may be referred to as “ETL17,” and is

an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

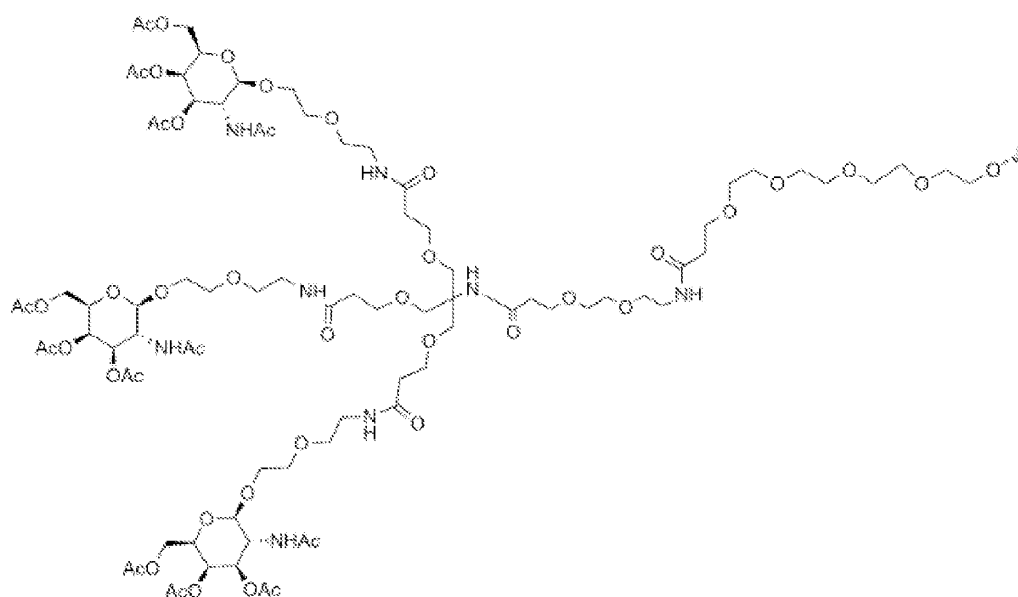
[00119] Some embodiments include the following, where the phosphate or “5'” indicates a connection to the oligonucleotide:



[00120] Some embodiments include the following, where the phosphate or “5'” indicates a connection to the oligonucleotide:

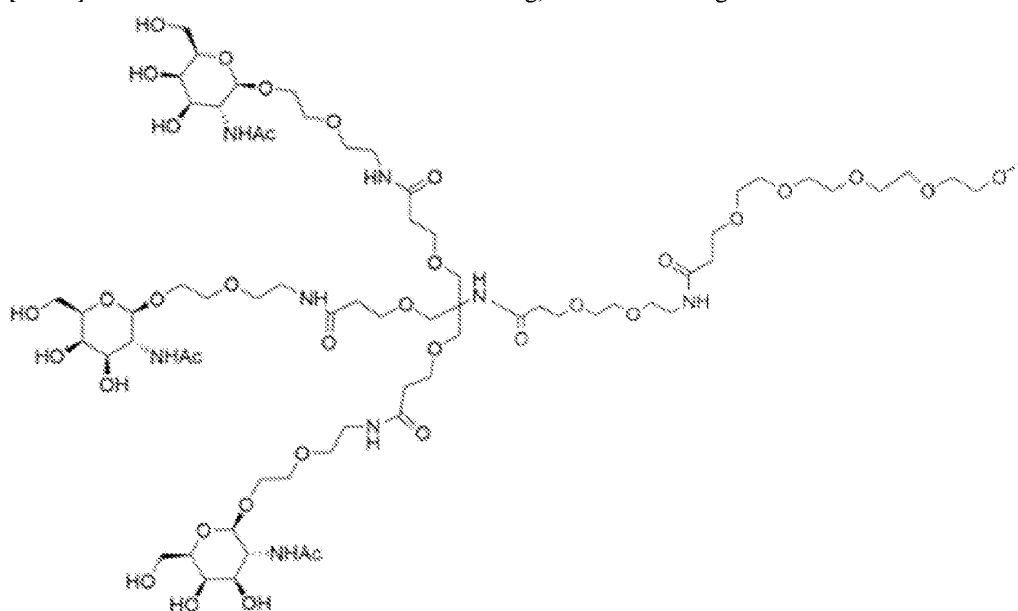


[00121] Some embodiments include the following, where J is the oligonucleotide:



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

[00122] Some embodiments include the following, where J is the oligonucleotide:



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

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

3. siRNA modification patterns

[00123] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises modification pattern 1S:

5'-NfsnsNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 3622), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 2S:

5'-nsnsnnNfnNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3623), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 3S: 5'-nsnsnnNfnNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3624), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 4S: 5'-NfsnsNfnNfnNfnNfnNfnNfnNfsnsnN-moiety-3' (SEQ ID NO: 3625), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 5S: 5'-nsnsnnNfnNfnNfnnnnnnnnsnsnN-moiety-3' (SEQ ID NO: 3626), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the moiety in modification pattern 4S or 5S is a lipid moiety. In some embodiments, the moiety in modification pattern 4S or 5S is a sugar moiety. In some embodiments, the sense strand comprises modification pattern 6S: 5'-NfsnsNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 3627), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 7S: 5'-nsnsnnNfnNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3628), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 8S: 5'-nsnsnnnnNfnNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3629), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 9S: 5'-nsnsnnnnNfnNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3630), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 10S: 5'-nsnsnnNfnNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3785), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00124] In some embodiments, the sense strand comprises modification pattern 11S: 5'-nsnsnnNfnnnNfnnnnnnnnsnsn-3' (SEQ ID NO: 3786), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00125] In some embodiments, the sense strand comprises modification pattern 12S: 5'-snnnnNfNfNfNfnnnnNfnnNfnnnsnsn-3' (SEQ ID NO: 3787), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00126] In some embodiments, the sense strand comprises modification pattern 13S: 5'-snnnnNfNfNfNfNfNfNfnnnnnsnsn-3' (SEQ ID NO: 3788), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00127] In some embodiments, the sense strand comprises modification pattern 14S: 5'-snnNfNfnnnnNfnnnnNfNfNfnnnsnsn-3' (SEQ ID NO: 3789), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00128] In some embodiments, the sense strand comprises modification pattern 15S: 5'-snnNfNfNfNfNfNfNfnnnnnsnsn-3' (SEQ ID NO: 3790), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 16S: 5'-snnnnNfNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3791), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 17S: 5'-snnnnNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3792), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 18S: 5'-snnnnNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3793), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 19S: 5'-snnnnNfnnnnNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3794), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 20S: 5'-snnnnNfNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3795), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 21S: 5'-snnnnNfNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3796), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 22S: 5'-snnnnNfNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3797), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 23S: 5'-snnnnNfNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3798), wherein "dT" is deoxythymidine, "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 24S: 5'-snnnnNfNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3799), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 25S: 5'-snnnnNfNfNfNfnnnnnnnnnsnsn-3' (SEQ ID NO: 3800), wherein "Nf" is a 2' fluoro-modified

nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 26S: 5'-snnnnnnNfnNfnfnnnnnnnnsnsn-3' (SEQ ID NO: 3801), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 27S: 5'-snnnnnnNfNfnNfnfnnnnnnsnsn-3' (SEQ ID NO: 3802), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 28S: 5'-snnnnnnNfnNfnNfnfnnnnsnsn-3' (SEQ ID NO: 3803), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 29S: 5'-snnnnnnNfNfnNfnfnnnnnnsnsn-3' (SEQ ID NO: 3804), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage.

[00129] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises modification pattern 1AS: 5’-nsNfsnNfnNfnNfnNfnNfnNfnnsnsn-3’ (SEQ ID NO: 3631), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 2AS: 5’-nsNfsnnNfnNfnNfnNfnNfnnsnsn-3’ (SEQ ID NO: 3632), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 3AS: 5’-nsNfsnnNfnnnnnNfnNfnnsnsn-3’ (SEQ ID NO: 3633), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 4AS: 5’-nsNfsnNfnNfnnnnnNfnNfnnsnsn-3’ (SEQ ID NO: 3634), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 5AS: 5’-nsNfsnnnnnnnnNfnNfnnsnsn-3’ (SEQ ID NO: 3635), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 6AS: 5’-nsNfsnnNfnNfnnnNfnNfnnsnsn-3’ (SEQ ID NO: 3636), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 7AS: 5’-nsNfsnNfnNfnNfnNfnNfnNfnNfnnsnsn-3’ (SEQ ID NO: 3637), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 8AS: 5’-nsNfsnnnnnnnnNfnnnnsnsn-3’ (SEQ ID NO: 3638), wherein “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage. In some

embodiments, the antisense strand comprises modification pattern 9AS:

5'-nNfnNfnNfnNfnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3639), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 10AS: 5'-

nsNfsnNfnnnNfnNfnNfnNfnNfnNfnnsn-3' (SEQ ID NO: 3805), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 11AS: 5'-

nsNfsnNfnnnNfnnNfnNfnNfnNfnNfnnsn-3' (SEQ ID NO: 3806), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 12AS: 5'-

nsNfsndTndNnNfnNfndNnNfndNnNfnsnsn-3' (SEQ ID NO: 3807), wherein "Nf" is a 2' fluoro-modified nucleoside, "dT" is deoxythymidine, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern

13AS: 5'-nsNfsndTndNnNfnNfndNndTndNndTnsnsn-3' (SEQ ID NO: 3808), wherein "Nf" is a 2' fluoro-modified nucleoside, "dT" is deoxythymidine, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern

14AS: 5'-nsNfsnnnnNfnnnnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3809), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 15AS: 5'-

dTsNfsnnnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 3810), wherein "Nf" is a 2' fluoro-modified nucleoside, "dT" is deoxythymidine, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern

16As: 5'-NfsNfsnnnnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 3811), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 17As: 5'-

nsNfsnnnNfnNfnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3812), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 18AS: 5'-

nsNfsnNfnNfnnnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3813), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 19AS: 5'-

nsNfsnNfnfnNfNfnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3814), wherein "NF" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 20AS: 5'-

nsNfsnNfnnnNfnnnnnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3815), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 21AS: 5'-

nsNfsnnnNfnNfnnnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 3816), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00130] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises pattern 1S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 2S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 3S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 4S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 5S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 6S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 7S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 8S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 9S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 10S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 11S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 12S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 13S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 14S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the sense strand comprises pattern 15S and the antisense strand comprises pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS,

[00131] In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, or 29S and the antisense strand comprises pattern 1AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S,

[illegible]

7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, or 29S and the antisense strand comprises pattern 19AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, or 29S and the antisense strand comprises pattern 209AS. In some embodiments, the sense strand comprises pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, or 29S and the antisense strand comprises pattern 21AS.

[00132] In some embodiments, the sense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS. In some embodiments, the antisense strand comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 156S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, or 29S. In some embodiments, the sense strand or the antisense strand comprises modification pattern ASO1.

[00133] In some embodiments, purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines.

[00134] In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[00135] In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2'-O-methyl modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2'-O-methyl modified purines, and pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines,

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

[00136] In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the sense strand comprise 2' fluoro modified purines.

[00137] In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines.

[00138] In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[00139] In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some

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

[00140] In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the antisense strand comprise 2' fluoro modified purines.

[00141] Disclosed herein, in some embodiments, are modified oligonucleotides. The modified oligonucleotide may be an siRNA that includes modifications to the ribose rings, and phosphate linkages. The modifications may be in particular patterns that maximize cell delivery, stability, and efficiency. The siRNA may also include a vinyl phosphonate and a hydrophobic group. These modifications may aid in delivery to a cell or tissue within a subject. The modified oligonucleotide may be used in a method such as a treatment method or a method of reducing gene expression.

[00142] In some embodiments, the oligonucleotide comprises a duplex consisting of 21 nucleotide single strands with base pairing between 19 of the base pairs. In some embodiments, the duplex comprises single-stranded 2 nucleotide overhangs at the 3' ends of each strand. One strand (antisense strand) is complementary to a FGG mRNA. Each end of the antisense strand has one to two phosphorothioate bonds. The 5' end has an optional phosphate mimic such as a vinyl phosphonate. In some embodiments, the oligonucleotide is used to knock down a FGG mRNA or a target protein. In some embodiments, the sense strand has the same sequence as the FGG mRNA. In some embodiments, there

are 1-2 phosphorothioates at the 3' end. In some embodiments, there are 1 or no phosphorothioates at the 5' end. In some embodiments, there is a hydrophobic conjugate of 12 to 25 carbons attached at the 5' end via a phosphodiester bond.

[00143] In some cases, the sense strand of any of the siRNAs comprises siRNA with a particular modification pattern. In some embodiments of the modification pattern, position 9 counting from the 5' end of the sense strand may have a 2'F modification. In some embodiments, when position 9 of the sense strand is a pyrimidine, then all purines in the sense strand have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense strand, then position 9 is the only position with a 2'F modification in the sense strand. In some embodiments, when position 9 and only one other base between positions 5 and 11 of the sense strand are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in the sense strand. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of the sense strand are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of the sense strand, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to any or all of these sense strand rules.

[00144] In some embodiments, when position 9 of the sense strand is a purine, then all purines in the sense strand have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense strand, then position 9 is the only position with a 2'F modification in the sense strand. In some embodiments, when position 9 and only one other base between positions 5 and 11 of the sense strand are purines, then both of these purines are the only two positions with a 2'F modification in the sense strand. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of the sense strand are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of the sense strand, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to any or all of these sense strand rules.

[00145] In some cases, position 9 of the sense strand can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of the sense strand. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to these sense strand rules.

[00146] In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to these sense strand rules.

[00147] Disclosed herein, in some embodiments are compositions comprising an oligonucleotide that targets FGG and when administered to a cell decreases expression of FGG, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the sense strand comprises a sense strand sequence described herein in which at least one internucleoside linkage is modified and at least one nucleoside is modified, or an sense strand sequence comprising 1 or 2 nucleoside substitutions, additions, or deletions of the oligonucleotide sequence in which at least one internucleoside linkage is modified and at least one nucleoside is modified, and wherein the antisense strand comprises an antisense strand sequence described herein in which at least one internucleoside linkage is modified and at least one nucleoside is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside substitutions, additions, or deletions of the antisense strand sequence in which at least one internucleoside linkage is modified and at least one nucleoside is modified. Some embodiments relate to methods that include administering the composition to a subject.

[00148] In some embodiments, the sense and/or antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to a sense and/or antisense strand sequence in any of **Tables 8-15, 18A, 22A, 26A, 31A, 33A, 37A, 42A, 66A or 81**. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any of **Tables 8-15, 18A, 22A, 26A, 31A, 33A, 37A, 42A, 66A or 81** or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any of **Tables 8-15, 18A, 22A, 26A, 31A, 33A, 37A, 42A, 66A or 81** or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in any of **Tables 8-15, 18A, 22A, 26A, 31A, 33A, 37A, 42A, 66A or 81**. The siRNA may include the same internucleoside linkage modifications or nucleoside modifications as those in any of **Tables 8-15, 18A, 22A, 26A, 31A, 33A, 37A, 42A, 66A or 81**. The siRNA may include any different internucleoside linkage modifications or nucleoside modifications different from those in any of **Tables 8-15, 18A, 22A, 26A, 31A, 33A, 37A, 42A, 66A or 81**. The siRNA may include some unmodified internucleoside linkages or nucleosides.

[00149] In some embodiments, the sense and/or antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to a sense and/or antisense strand sequence in **Table 8A**. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8A** or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8A** or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8A**. The siRNA may include the same internucleoside linkage modifications or nucleoside modifications as those in **Table 8A**. The siRNA may include any

different internucleoside linkage modifications or nucleoside modifications different from those in **Table 8A**. The siRNA may include some unmodified internucleoside linkages or nucleosides.

[00150] In some embodiments, the sense and/or antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to a sense and/or antisense strand sequence in **Table 8B**. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8B** or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8B** or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8B**. The siRNA may include the same internucleoside linkage modifications or nucleoside modifications as those in **Table 8B**. The siRNA may include any different internucleoside linkage modifications or nucleoside modifications different from those in **Table 8B**. The siRNA may include some unmodified internucleoside linkages or nucleosides.

[00151] In some embodiments, the sense and/or antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to a sense and/or antisense strand sequence in **Table 81**. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 81** or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 81** or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 81**. The siRNA may include the same internucleoside linkage modifications or nucleoside modifications as those in **Table 81**. The siRNA may include any different internucleoside linkage modifications or nucleoside modifications different from those in **Table 81**. The siRNA may include some unmodified internucleoside linkages or nucleosides.

[00152] In some embodiments, the sense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOS: 3591-3594. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3591-3594, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3591-3594, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3591-3594. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NOS: 3591-3594. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00153] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3591. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3591, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3591, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3591. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3591. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00154] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3592. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3592, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3592, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3592. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3592. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00155] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3593. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3593, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3593, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3593. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3593. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00156] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3594. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3594, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3594, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3594. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3594. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00157] In some embodiments, the sense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at

least 95% identical, to any one of SEQ ID NOs: 3641-3676. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3641-3676, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3641-3676, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3641-3676. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NOS: 3641-3676. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00158] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3651. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3651, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3651, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3651. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3651. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00159] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3652. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3652, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3652, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3652. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3652. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00160] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3654. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3654, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3654, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3654. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3594. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00161] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3675. In some embodiments, the sense strand comprises the nucleoside sequence

of SEQ ID NO: 3675, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3675, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 3675. The sense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3675. The sense strand may include some unmodified internucleoside linkages or nucleosides. The sense strand may include GalNAc1 or another GalNAc moiety.

[00162] In some embodiments, the antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOS: 3595-3598. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3595-3598, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3595-3598, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3595-3598. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NOS: 3595-3598. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00163] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3595. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3595, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3595, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3595. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3595. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00164] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3596. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3596, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3596, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3596. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3596. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00165] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3597. In some embodiments, the antisense strand comprises the nucleoside

sequence of SEQ ID NO: 3597, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3597, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3597. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3597. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00166] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3598. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3598, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3598, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3598. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3598. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00167] In some embodiments, the antisense strand comprises a nucleoside sequence at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to any one of SEQ ID NOS: 3677-3712. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3677-3712, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3677-3712, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 3677-3712. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NOS: 3677-3712. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00168] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3687. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3687, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3687, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3687. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3687. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00169] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3688. In some embodiments, the antisense strand comprises the nucleoside

sequence of SEQ ID NO: 3688, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3688, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3688. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3688. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00170] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3690. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3690, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3690, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3690. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3690. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

[00171] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 3747. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3747, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3747, and 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 3747. The antisense strand may include any different internucleoside linkage modifications or nucleoside modifications different from those in SEQ ID NO: 3747. The antisense strand may include some unmodified internucleoside linkages or nucleosides. The antisense strand may include a GalNAc moiety.

4. ASO modification patterns

[00172] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO comprises modification pattern ASO1:

5'-nsnsnsnsnsdNsdNsdNsdNsdNsdNsdNsdNsdNsdNsnsnsnsn-3' (SEQ ID NO: 3640), wherein "dN" is any deoxynucleotide, "n" is a 2'-O-methyl or 2'-O-methoxyethyl-modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the ASO comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 16S, 17S, 18S, 19S, 20S, 21S, 22S, 23S, 24S, 25S, 28S, 29S, 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, 15AS, 16AS, 17AS, 18AS, 19AS, 20AS, or 21AS.

D. Formulations

[00173] In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition is sterile. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[00174] In some embodiments, the pharmaceutically acceptable carrier comprises water. In some embodiments, the pharmaceutically acceptable carrier comprises a buffer. In some embodiments, the pharmaceutically acceptable carrier comprises a saline solution. In some embodiments, the pharmaceutically acceptable carrier comprises water, a buffer, or a saline solution. In some embodiments, the composition comprises a liposome. In some embodiments, the pharmaceutically acceptable carrier comprises liposomes, lipids, nanoparticles, proteins, protein-antibody complexes, peptides, cellulose, nanogel, or a combination thereof.

II. METHODS AND USES

[00175] Disclosed herein, in some embodiments, are methods of administering a composition described herein to a subject. Some embodiments relate to use a composition described herein, such as administering the composition to a subject.

[00176] Some embodiments relate to a method of treating a disease or disorder (e.g., mental disorder (e.g., psychiatric disorder or neurological disorder)) in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of treatment. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration treats the disorder in the subject. In some embodiments, the composition treats the disorder in the subject.

[00177] In some embodiments, the treatment comprises prevention, inhibition, or reversion of the disorder (e.g., mental disorder (e.g., psychiatric disorder or neurological disorder)) in the subject. Some embodiments relate to use of a composition described herein in the method of preventing, inhibiting, or reversing the disorder. Some embodiments relate to a method of preventing, inhibiting, or reversing a disorder in a subject in need thereof. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents, inhibits, or reverses the disorder in the subject. In some embodiments, the composition prevents, inhibits, or reverses the disorder in the subject.

[00178] Some embodiments relate to a method of preventing a disorder (e.g., mental disorder (e.g., psychiatric disorder or neurological disorder)) in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of preventing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents the disorder in the subject. In some embodiments, the composition prevents the disorder in the subject.

[00179] Some embodiments relate to a method of inhibiting a disorder (e.g., mental disorder (e.g., psychiatric disorder or neurological disorder)) in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of inhibiting the disorder. Some embodiments

include administering a composition described herein to a subject with the disorder. In some embodiments, the administration inhibits the disorder in the subject. In some embodiments, the composition inhibits the disorder in the subject.

[00180] Some embodiments relate to a method of reversing a disorder (e.g., mental disorder (e.g., psychiatric disorder or neurological disorder)) in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of reversing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration reverses the disorder in the subject. In some embodiments, the composition reverses the disorder in the subject.

[00181] In some embodiments, the administration is systemic. In some embodiments, the administration is intravenous. In some embodiments, the administration is by injection.

A. Disorders

[00182] Some embodiments of the methods described herein include treating a disorder in a subject in need thereof. A disorder can include a disease. In some embodiments, the disorder is a mental disorder. In some embodiments, the mental disorder is a psychiatric disorder or neurological disorder. The psychiatric disorder or neurological disorder may comprise a hepatic disorder, a brain disorder, a CNS disorder, a CSF disorder, or a combination thereof.

[00183] In some embodiments, the disorder comprises a psychiatric disorder. Non-limiting examples of psychiatric disorders include depressive disorders, such as major depressive disorder, persistent depressive disorder, treatment resistant depression and signs or symptoms of depression. Further non-limiting examples of psychiatric disorders include post-traumatic stress disorder, mood disorders, anxiety disorders (e.g., generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social phobia, etc.), eating disorders, substance-use disorders (e.g., alcohol use disorders, prescription medicines use disorders, illegal drug use disorders, psychoactive substance-use disorders, etc.) bipolar disorder, personality disorders, schizophrenia and schizoaffective disorders. .

[00184] In some embodiments, the disorder is a depressive disorder. Examples of depressive disorders include major depressive disorder, persistent depressive disorder, or treatment resistant depression. In some embodiments, the depressive disorder comprises or consists of major depressive disorder. In some embodiments, the depressive disorder comprises or consists of persistent depressive disorder. In some embodiments, the depressive disorder comprises or consists of treatment resistant depression. In some embodiments, the depressive disorder is treatment resistant depression. Treatment resistant depression may include depression that does not respond (e.g., within an acceptable period of time) to first, second, or third line treatments. In some embodiments, the disorder includes a sign or symptom of depression. Exemplary signs or symptoms of depression may include a persistent feeling of sadness or loss of interest, apathy, feelings of hopelessness and sadness, anxiety, agitation, and restlessness. Exemplary signs or symptoms of depression may be any sign or symptom of depression within the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which is hereby incorporated by reference.

[00185] In some embodiments, the disorder comprises post-traumatic stress disorder (PTSD). Exemplary signs or symptoms of PTSD include recurrent, unwanted distressing memories of the traumatic event, flashbacks, upsetting dreams or nightmares about the traumatic event, negative thoughts about yourself, other people or the world, memory problems, difficulty experiencing positive emotions, or feeling emotionally numb. Exemplary signs or symptoms of PTSD may be any sign or symptom of PTSD within the DSM-5.

[00186] In some embodiments, the disorder comprises mood disorders. An exemplary mood disorder includes dysthymia. In some embodiments, the disorder comprises anxiety disorders. Exemplary anxiety disorders include generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, social phobias, and social anxiety disorder. Signs or symptoms of anxiety disorders include a feeling of restlessness, being easily fatigued, having difficulty concentration, and being irritable. Exemplary signs or symptoms of anxiety disorders (e.g., GAD, OCT, etc.) may be any sign or symptom of anxiety disorders within the DSM-5.

[00187] In some embodiments, the disorder comprises eating disorders. Exemplary eating disorders include anorexia nervosa, bulimia nervosa, and binge-eating disorder. Exemplary signs and symptoms of eating disorders include extremely restricted eating, emaciation, intense fear of gaining weight, brittle nails and hair, eating unusually large amounts of food in a specific amount of time, such as a 2-hour period, eating even when you're full or not hungry, and eating until you're uncomfortably full. Exemplary signs or symptoms of eating disorders may be any sign or symptom of eating disorders within the DSM-5.

[00188] In some embodiments, the disorder comprises substance-use disorders. Exemplary substance-use disorders include alcohol-use disorder, prescription drug use disorder, illegal drug use disorder, solvent abuse, and "legal high" abuse. Exemplary signs and symptoms of substance-use disorders include intense urges for the substance that block out other thoughts, needing more of the substance to get the same effect over time, and failure in attempts to stop using the substance. Exemplary signs or symptoms of substance-use disorders may be any sign or symptom of substance-use disorders within the DSM-5.

[00189] In some embodiments, the disorder comprises bipolar disorder. In some embodiments, the bipolar disorder comprises bipolar I disorder. In some embodiments, the bipolar disorder comprises bipolar II disorder. In some embodiments, the bipolar disorder comprises cyclothymic bipolar disorder. In some embodiments, the bipolar disorder comprises mixed feature bipolar disorder. Exemplary signs and symptoms of bipolar disorder include experiencing a manic episode and experiencing a major depressive episode. Exemplary signs or symptoms of bipolar disorder may be any sign or symptom of bipolar disorder within the DSM-5.

[00190] In some embodiments, the disorder comprises a personality disorder. Exemplary personality disorders include borderline personality disorder, antisocial personality disorder, histrionic personality disorder, narcissistic personality disorder, avoidant personality disorder, and schizoid personality disorder. Exemplary signs and symptoms of personality disorders include impulsive and risky behavior, unstable or fragile self-image, up and down moods, and suicidal behavior or threats of self-injury. Exemplary signs or symptoms of personality disorder may be any sign or symptom of personality disorder within the DSM-5.

[00191] In some embodiments, the disorder comprises schizophrenia. Exemplary schizophrenia signs and symptoms include delusions, hallucinations, disorganized thinking, and loss of interest or motivation in life. In some embodiments, the signs and symptoms comprise positive symptoms (e.g., hallucinations or delusions). In some embodiments, the signs and symptoms comprise negative symptoms (e.g., lack of interest or emotionally flat). Exemplary signs or symptoms of schizophrenia may be any sign or symptom of schizophrenia within the DSM-5.

[00192] In some embodiments, the disorder comprises schizoaffective disorders. Exemplary schizoaffective disorders include the bipolar type schizoaffective disorder and depressive type schizoaffective disorder. Exemplary signs and symptoms of schizoaffective disorders include delusions, hallucinations, impaired communication, and bizarre or unusual behavior. Exemplary signs or symptoms of schizoaffective disorders may be any sign or symptom of schizoaffective disorders within the DSM-5.

[00193] In some embodiments, the disorder comprises a neurological disorder. Non-limiting examples of neurological disorders include Alzheimer's disease, dementia, cognitive decline, vascular dementia. Further non-limiting examples of neurological disorders include headache, migraine (e.g., with aura and/or without aura), chronic pain, fibromyalgia, chronic fatigue syndrome (e.g. myalgic encephalomyelitis), motor neuron disease (e.g., Amyotrophic Lateral Sclerosis (ALS)).

[00194] In some embodiments, the disorder comprises dementia. In some embodiments, dementia comprises vascular dementia. In some embodiments, dementia comprises lewy body dementia. In some embodiments, dementia comprises frontotemporal dementia. In some embodiments, dementia comprises Alzheimer's disease. In some embodiments, dementia comprises mixed dementia. Exemplary signs and symptoms of dementia include memory loss, difficulty communicating, difficulty with visual and spatial abilities, difficulty reasoning or problem-solving, difficulty with coordination and motor functions, and confusion and disorientation.

[00195] In some embodiments, Alzheimer's disease comprises early-onset Alzheimer's disease. Early-onset Alzheimer's disease may occur in subjects under the age of 65 years old. In some embodiments, Alzheimer's disease comprises late-onset Alzheimer's disease. In some embodiments, Alzheimer's disease comprises common Alzheimer's disease. In some embodiments, Alzheimer's disease comprises genetic Alzheimer's disease. Exemplary signs and symptoms of Alzheimer's disease include increased memory loss and confusion, inability to learn new things, difficulty with language, difficulty organizing thoughts and thinking logically, shortened attention span, and problems coping with new situations.

[00196] In some embodiments, the disorder comprises delirium. Exemplary forms of delirium include hyperactive delirium, hypoactive delirium, and mixed delirium. Exemplary signs and symptoms of delirium include agitation, disorientation, delusional thoughts, hallucinations, poor memory, difficulty speaking and trouble understanding speech.

[00197] In some embodiments, the disorder comprises cognitive decline. Exemplary forms of cognitive decline include mild cognitive impairment, dementia, primary progressive aphasia, corticobasal degeneration, primary progressive aphasia, and progressive supranuclear palsy. Exemplary signs and

symptoms of cognitive decline include forgetfulness, feelings of being overwhelmed, difficulty understanding directions or instructions, inability to organize tasks, and an increased impulsiveness.

[00198] In some embodiments, the disorder comprises a headache. In some embodiments, the headache comprises a migraine (e.g., with aura or without aura). Headaches may include sinus headaches, tension headache, migraine, and cluster headache. Exemplary signs and symptoms of headaches include pain (e.g., deep and constant) in the cheekbones, forehead, bridge of the nose, the cranium, or the back of the neck, aura, photophobia, phonophobia, and emesis.

[00199] In some embodiments, the disorder comprises chronic pain. In some embodiments, chronic pain comprises fibromyalgia. Exemplary signs and symptoms of fibromyalgia include muscular pain, fatigues, depression, anxiety, sleeplessness, headache, and difficulty concentrating. Exemplary chronic pain disorders include postsurgical pain, post-trauma pain, low back pain, cancer pain, arthritis pain, muscular pain, and neuropathic pain (e.g., diabetic neuropathy).

[00200] In some embodiments, the disorder comprises chronic fatigue syndrome (also referred to as myalgic encephalomyelitis). Exemplary signs and symptoms of chronic fatigue syndrome include extreme fatigue that lasts for extended periods of time (e.g., for at least six months) that cannot be fully explained by an underlying medical condition, fatigue that worsens with physical or mental activity, pain (e.g., joint or muscular), malaise, forgetfulness, anxiety, and depression.

[00201] In some embodiments, the disorder comprises a motor neuron disease. In some embodiments, the motor neuron disease is amyotrophic lateral sclerosis (ALS). Exemplary forms of motor neuron diseases include progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), ALS, and primary lateral sclerosis (PLS). Exemplary signs and symptoms of motor neuron diseases (e.g., ALS) include motor control difficulties (e.g., difficulty walking or completing normal daily activities), muscular weakness, slurred speech, difficulty swallowing, muscle cramps and twitching (e.g., in the arms, shoulders, or tongue), and inappropriate crying, laughing or yawning.

[00202] In some embodiments, the disorder comprises a coagulation or clotting disorder. In some embodiments, the coagulation or clotting disorder comprises Hemophilia, Von Willebrand disease or clotting factor deficiencies. In some embodiments, the coagulation or clotting disorder comprises a thrombophilia. In some embodiments, the thrombophilia comprises an inherited thrombophilia. In some embodiments, the thrombophilia comprises an acquired thrombophilia. In some embodiments, the coagulation or clotting disorder comprises a hypercoagulable state. In some embodiments, the hypercoagulable state comprises cancer. In some embodiments, the hypercoagulable state comprises atrial fibrillation. In some embodiments, the hypercoagulable states comprises a post surgical period or immobility. In some embodiments, the coagulation or clotting disorder comprises arterial thrombosis or thromboembolism. In some embodiments, the coagulation or clotting disorder comprises venous thrombosis or thromboembolism. In some embodiments, the venous thromboembolism comprises deep venous thrombosis. In some embodiments, the venous thromboembolism comprises pulmonary embolism. In some embodiments, the venous thromboembolism comprises thrombophlebitis.

[00203] In some cases, the disorder may be diagnosed with the use of a questionnaire or a scoring system. In some cases, the disorder is diagnosed according to DSM-5 criteria. In some cases, the disorder is diagnosed by a healthcare professional (e.g., physician or the like).

[00204] In some embodiments, the disorder comprises one or more disorders (e.g., any of the disorders disclosed herein). In some embodiments, the disorder comprises two disorders. In some embodiments, the disorder comprises three disorders. In some embodiments, the disorder comprises four disorders. In some embodiments, the disorder comprises five disorders.

B. Subjects

[00205] Some embodiments of the methods described herein include treatment of a subject. Non-limiting examples of subjects include vertebrates, animals, mammals, dogs, cats, cattle, rodents, mice, rats, primates, monkeys, and humans. In some embodiments, the subject is a vertebrate. In some embodiments, the subject is an animal. In some embodiments, the subject is a mammal. In some embodiments, the subject is a dog. In some embodiments, the subject is a cat. In some embodiments, the subject is a cattle. In some embodiments, the subject is a mouse. In some embodiments, the subject is a rat. In some embodiments, the subject is a primate. In some embodiments, the subject is a monkey. In some embodiments, the subject is an animal, a mammal, a dog, a cat, cattle, a rodent, a mouse, a rat, a primate, or a monkey. In some embodiments, the subject is a human.

[00206] In some embodiments, the subject is male. In some embodiments, the subject is female. In some embodiments, the subject is an adult (e.g. at least 18 years old). In some embodiments, the subject is 45 years old or greater. In some embodiments, the subject is 50 years old or greater. In some embodiments, the subject is 55 years old or greater. In some embodiments, the subject is 60 years old or greater. In some embodiments, the subject is 65 years old or greater. In some embodiments, the subject is 70 years old or greater. In some embodiments, the subject is 75 years old or greater. In some embodiments, the subject is 80 years old or greater. In some embodiments, the subject is 85 years old or greater.

[00207] In some embodiments, the subject has a body mass index (BMI) of 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more, or a range defined by any two of the aforementioned integers. In some embodiments, the subject is overweight. In some embodiments, the subject has a BMI of 25 or more. In some embodiments, the subject has a BMI of 25-29. In some embodiments, the subject is obese. In some embodiments, the subject has a BMI of 30 or more. In some embodiments, the subject has a BMI of 30-39. In some embodiments, the subject has a BMI of 40-50. In some embodiments, the subject has a BMI of 25-50.

[00208] In some embodiments, the subject has a personal history with the disorder. In some embodiments, the subject has a familial history with the disorder. In some embodiments, the subject is at high risk of contracting the disorder.

[00209] In some embodiments, the subject has a coagulation or clotting disorder. In some embodiments, the coagulation or clotting disorder comprises Hemophilia, Von Willebrand disease or clotting factor deficiencies. In some embodiments, the subject has a thrombophilia. In some embodiments,

the thrombophilia comprises an inherited thrombophilia. In some embodiments, the thrombophilia comprises an acquired thrombophilia. In some embodiments, the subject has a hypercoagulable state. In some embodiments, the hypercoagulable state comprises cancer. In some embodiments, the hypercoagulable state comprises atrial fibrillation. In some embodiments, the hypercoagulable states comprises a post surgical period or immobility. In some embodiments, the subject has arterial thrombosis or thromboembolism. In some embodiments, the subject has venous thrombosis or thromboembolism. In some embodiments, the venous thromboembolism comprises deep venous thrombosis. In some embodiments, the venous thromboembolism comprises pulmonary embolism. In some embodiments, the venous thromboembolism comprises thrombophlebitis.

C. Baseline measurements

[00210] Some embodiments of the methods described herein include obtaining a baseline measurement from a subject. In some embodiments, the baseline measurement is a mental disorder (e.g., psychiatric or neurological disorder) baseline measurement. For example, in some embodiments, a baseline measurement is obtained from the subject prior to treating the subject. Non-limiting examples of baseline measurements include a baseline measurement of Montgomery-Asberg Depression Rating Scale (MADRS); a baseline Hamilton Depression Rating Scale-17 (e.g., scale ranges from 0 to 52 with a higher score indicating worsening symptoms of depression); baseline anxiety symptoms and/or signs, baseline eating disorder symptoms and/or signs, baseline substance-use disorder symptoms and/or signs, baseline post-traumatic stress disorder symptoms and/or signs, baseline bipolar disorder symptoms and/or signs, baseline schizophrenia symptoms and/or signs, and baseline psychosis symptoms and/or signs. In some embodiments, the baseline measurement includes an aspect of any of **Tables 1A-1C and 2A-2B**. The baseline measurement may include a baseline fibrinogen measurement, a baseline FGG mRNA measurement, or a baseline FGG protein measurement. The baseline measurement may include a baseline clotting measurement, a baseline prothrombin time (PT) measurement, a baseline International Normalized Ratio (INR) measurement, or a baseline activated partial thromboplastin time (aPTT) measurement.

[00211] In some embodiments, the baseline measurement is obtained directly from the subject. In some embodiments, the baseline measurement is obtained by observation of the subject. In some embodiments, the baseline measurement is obtained by questioning the subject. In some embodiments, the baseline measurement is obtained by the subject filling out a questionnaire.

[00212] In some embodiments, the baseline measurement is a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score. The MADRS scale may range from 0 to 60 with a higher score indicating worsening symptoms of depression. The MADRS generally includes a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders. It was designed as an adjunct to the HDRS to be, in some cases, more sensitive to changes brought on by antidepressants or other forms of treatment. A higher MADRS score indicates more severe depression than a lower score. The overall score ranges from 0 to 60. Example cutoff points are as follows:

- 0 to 6 – normal/absent symptoms
- 7 to 19 – mild depression
- 20 to 34 – moderate depression, and
- >34 – severe depression.

[00213] In some embodiments, the baseline MADRS score comprises a numerical value such as a number of points. In some embodiments, the numerical value is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60, or a range defined by any two of the aforementioned numerical values. In some embodiments, the numerical value is 1-5. In some embodiments, the numerical value is 6-10. In some embodiments, the numerical value is 11-15. In some embodiments, the numerical value is 16-20. In some embodiments, the numerical value is 21-25. In some embodiments, the numerical value is 26-30. In some embodiments, the numerical value is 31-35. In some embodiments, the numerical value is 36-40. In some embodiments, the numerical value is 41-45. In some embodiments, the numerical value is 46-50. In some embodiments, the numerical value is 51-55. In some embodiments, the numerical value is 56-60. In some embodiments, the numerical value is 1-60. In some embodiments, the baseline MADRS score comprises a baseline subscore such as a baseline apparent sadness score, a baseline reported sadness score, a baseline inner tension score, a baseline reduced sleep score, a baseline reduced appetite score, a baseline concentration difficulties score, a baseline lassitude score, a baseline inability to feel score, a baseline pessimistic thoughts score, or a baseline suicidal thoughts score. Each baseline subscore may comprise a numerical value of 0, 1, 2, 3, 4, 5, or 6, or a range of such numerical values. In some embodiments, the baseline MADRS score comprises a numerical value at or above a threshold numerical value that is indicative of a depressive disorder. For example, the subject may be depressed prior to treatment and have a baseline MADRS score of 7-60. The subject may have mild depression prior to treatment and have a baseline MADRS score of 7-19. The subject may have moderate depression prior to treatment and have a baseline MADRS score of 20-34. The subject may have severe depression prior to treatment and have a baseline MADRS score over 34. In some embodiments, one or more of the baseline subscores comprise a numerical value at or above a threshold numerical value that is indicative of the depressive disorder.

[00214] In some embodiments, the baseline measurement comprises a baseline Hamilton Depression Rating Scale (HDRS) score. The HDRS typically includes a multiple item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery. The questionnaire is usually designed for adults and is used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. The subject is usually rated by a clinician on 17 to 29 items (depending on version) scored either on a 3-point or 5-point Likert-type scale. In some cases, the HDRS includes 17 items (HDRS₁₇). Other variations may be used, such as those that include more than 17 items. For example, up to 29 items may be used in some cases (HDRS₂₉). For the 17-item version, a score of 0-7 is typically considered to be normal while a score of 20 or higher may indicate moderate or severe depression.

[00215] In some embodiments, the baseline HDRS score comprises a numerical value such as a number of points. In some embodiments, the numerical value is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, or a range defined by any two of the aforementioned numerical values. In some embodiments, the numerical value is 1-5. In some embodiments, the numerical value is 6-10. In some embodiments, the numerical value is 11-15. In some embodiments, the numerical value is 16-20. In some embodiments, the numerical value is 21-25. In some embodiments, the numerical value is 26-30. In some embodiments, the numerical value is 31-35. In some embodiments, the numerical value is 36-40. In some embodiments, the numerical value is 41-45. In some embodiments, the numerical value is 46-50. In some embodiments, the numerical value is 51 or 52. In some embodiments, the numerical value is 1-50. In some embodiments, the numerical value is 1-52. In some embodiments, the baseline HDRS score comprises a baseline subscore such as a baseline depressed mood score, a baseline feelings of guilt score, a baseline suicide score, a baseline insomnia early in the night score, a baseline insomnia in the middle of the night score, a baseline insomnia in early hours of the morning score, a baseline work and activities score, a baseline retardation score, a baseline agitation score, a baseline anxiety psychic score, a baseline anxiety somatic score, a baseline somatic symptoms of gastrointestinal score, a baseline general somatic score, a baseline genital symptoms score, a baseline hypochondriasis score, a baseline loss of weight score, or a baseline insight score. Baseline subscores may comprise a numerical value of 0, 1, or 2, or a range of such numerical values. Baseline subscores may comprise a numerical value of 0, 1, 2, 3, or 4, or a range of such numerical values. In some embodiments, the baseline HDRS score comprises a numerical value at or above a threshold numerical value that is indicative of a depressive disorder. For example, a HDRS score of 20 or higher may be indicative of moderate to severe depression. In some cases, the subject is depressed prior to treatment and has an HDRS score above 19. In some cases, the subject is at least mildly depressed prior to treatment and has an HDRS score above 7. In some embodiments, the baseline subscore comprises a numerical value at or above a threshold numerical value that is indicative of the depressive disorder.

[00216] In some embodiments, the baseline measurement is a baseline anxiety measurement. The baseline anxiety measurement may include a baseline assessment of a sign or symptom of anxiety (e.g., a baseline anxiety sign or symptom). Examples of signs or symptoms of anxiety include stress (e.g. stress that's out of proportion to the impact of an event), worry (for example, inability to set aside a worry), or restlessness. In some cases, the symptom of anxiety includes one or more behavioral symptoms such as hypervigilance, irritability, or restlessness. In some cases, the symptom of anxiety includes one or more cognitive symptoms such as lack of concentration, racing thoughts, or unwanted thoughts. In some cases, the symptom of anxiety includes one or more whole body symptoms such as fatigue or sweating. In some cases, the symptoms of anxiety include any of excessive worry, fear, feeling of impending doom, insomnia, nausea, palpitations, or trembling. In some embodiments, the symptom includes one or more panic attacks. The baseline assessment may include an amount, frequency, duration, or intensity of the anxiety or symptoms of anxiety. The baseline assessment may include an amount of time since

experiencing the anxiety or symptoms. The baseline assessment may include a frequency of experiencing the anxiety or symptoms.

[00217] In some embodiments, the baseline measurement is a baseline eating disorder measurement. In some embodiments, the baseline measurement is a baseline eating disorder sign or symptom. Examples of eating disorders include anorexia, bulimia, binge eating disorder, pica, rumination, or avoidant eating disorder. In some embodiments, the eating disorder includes anorexia nervosa. In some embodiments, the eating disorder includes bulimia. In some embodiments, the eating disorder includes binge eating. In some embodiments, the eating disorder includes pica. The baseline eating disorder measurement may include a baseline assessment of a sign or symptom of eating disorder (e.g., a baseline eating disorder sign or symptom). Some examples of symptoms of an eating disorder comprising anorexia nervosa include being considerably underweight compared with people of similar age and height, very restricted eating patterns, an intense fear of gaining weight or persistent behaviors to avoid gaining weight despite being underweight, a relentless pursuit of thinness and unwillingness to maintain a healthy weight, a heavy influence of body weight or perceived body shape on self-esteem, a distorted body image, or denial of being seriously underweight. The baseline assessment may include an amount, frequency, duration, or intensity of the engaging in the eating disorder or experiencing symptoms of the eating disorder. The baseline assessment may include an amount of time since engaging in the eating disorder or experiencing symptoms of the eating disorder. The baseline assessment may include a frequency of engaging in the eating disorder or experiencing symptoms of the eating disorder.

[00218] In some embodiments, the baseline measurement is a baseline substance-use measurement. In some embodiments, the baseline substance-use measurement includes a baseline determination of a level of addiction to an addictive substance. Examples of addictive substances include alcohol, antianxiety drugs, sedative drugs, caffeine, cannabis (e.g. including marijuana or synthetic cannabinoids), hallucinogens (e.g. LSD, phencyclidine, or psilocybin), inhalants (e.g. paint thinner or some glues), opioids (e.g. fentanyl, morphine, or oxycodone), stimulants (e.g. amphetamines or cocaine), tobacco, or anabolic steroids. The baseline determination of a level of addiction to an addictive substance may include a questionnaire or assessment. The baseline determination of a level of addiction to an addictive substance may include an amount of time since ingesting the addictive substance. The baseline determination of a level of addiction to an addictive substance may include a frequency of ingesting the addictive substance. The baseline assessment may include an amount, frequency, duration, or intensity of the engaging in the substance-use disorder or experiencing symptoms of the substance-use disorder. The baseline assessment may include an amount of time since engaging in the substance-use disorder or experiencing symptoms of the substance-use disorder. The baseline assessment may include a frequency of engaging in the substance-use disorder or experiencing symptoms of the substance-use disorder. The baseline assessment may include signs or symptoms of the substance-use disorder. Exemplary signs and symptoms may include feelings of regularly (e.g., daily) substance-use, intense urges for the substance, needing more of the substance to obtain a previously obtained effect, and continuing to use the substance although use of the substance is known to cause problems in normal life activities.

[00219] In some embodiments, the baseline measurement comprises a baseline post-traumatic stress disorder (PTSD) measurement. In some embodiments, the baseline PTSD measurement includes a baseline determination of the level of severity of PTSD. The baseline assessment of a sign or symptom of PTSD may include the number of signs or symptoms of PTSD. The baseline determination of the level of severity of PTSD may include the time since last experiencing a PTSD flashback (e.g., reliving the traumatic event as if it were happening again), nightmare, or severe anxiety. The baseline assessment may include a frequency in PTSD related flashbacks, nightmares, or severe anxiety episodes. The baseline assessment may include a severity of a sign or symptom of PTSD. The baseline assessment may include a frequency of a sign or symptom of PTSD. Exemplary signs and symptoms of PTSD may include intrusive memories (e.g., recurrent, unwanted distressing memories of a traumatic event, severe emotional distress or physical reactions to something that reminiscent of the traumatic event, attempts to avoid thinking or talking about the traumatic event, avoiding places, activities or people reminiscent of the traumatic event, thoughts of hopelessness, memory problems, difficulty maintaining close relationships, and feeling a lack of interest in activities that were once enjoyed.

[00220] In some embodiments, the baseline measurement comprises a baseline bipolar disorder measurement. In some embodiments, the baseline bipolar disorder measurement is a sign or symptom of bipolar disorder. The baseline assessment of a sign or symptom of bipolar disorder may include a frequency of a sign or symptom of bipolar disorder. The baseline assessment of a sign or symptom of bipolar disorder may include a severity of a sign or symptom of bipolar disorder. The baseline assessment of a sign or symptom of bipolar disorder may include the number of signs or symptoms of bipolar disorder. Exemplary signs and symptoms of bipolar disorder include any of the bipolar signs and symptoms disclosed herein, including, manic episodes (e.g., experiencing feelings of increased activity, energy, or agitation, an exaggerated sense of well-being and self-confidence, a decreased need for sleep, racing thoughts, distractibility, and a decreased ability to control impulses), and major depressive episodes (e.g., experiencing a depressed mood, marked loss of interest or feelings of pleasure, fatigue or loss of energy, feelings of guilt or worthlessness, and a decreased ability to think or concentrate).

[00221] In some embodiments, the baseline measurement comprises a baseline schizophrenia measurement. In some embodiments, the baseline schizophrenia measurement is a sign or symptom of schizophrenia. The baseline assessment of a sign or symptom of schizophrenia may include a frequency of a sign or symptom of schizophrenia. The baseline assessment of a sign or symptom of schizophrenia may include a severity of a sign or symptom of schizophrenia. The baseline assessment of a sign or symptom of schizophrenia may include the number of signs or symptoms of schizophrenia. Exemplary signs and symptoms of schizophrenia may include delusions, hallucinations, disorganized thoughts and speech, disorganized or abnormal motor behavior, and negative symptoms (e.g., social withdrawal, anhedonia, avolition, decreased sense of purpose, lack of interest in activities, flat affect, lack of eye contact, and physical inactivity).

[00222] In some embodiments, the baseline measurement comprises a baseline psychosis measurement. In some embodiments, the baseline psychosis measurement is a baseline sign or symptom

of psychosis (e.g., baseline psychosis sign or symptom). The baseline assessment of a sign or symptom of psychosis may include a frequency of a sign or symptom of psychosis. The baseline assessment of a sign or symptom of psychosis may include a severity of a sign or symptom of psychosis. The baseline assessment of a sign or symptom of psychosis may include the number of signs or symptoms of psychosis. Exemplary signs and symptoms of psychosis may include difficulty concentrating, depressed mood, anxiety, excessive suspiciousness, delusions, and hallucinations.

[00223] In some embodiments, the baseline measurement comprises a baseline measurement of a neurological disorder. Non-limiting examples of baseline measurements of neurological disorders include a baseline measurement of cognitive function, a baseline measurement of CNS amyloid plaque(s) (e.g., accumulation), a baseline measurement of CNS tau accumulation, a baseline measurement of CSF beta-amyloid 42 (e.g., accumulation), a baseline measurement of CSF tau (e.g., accumulation), a baseline measurement of CSF phospho-tau (e.g., accumulation), a baseline measurement of Lewy bodies (e.g., accumulation), or a baseline measurement of CSF alpha-synuclein (e.g., accumulation). Further non-limiting examples of baseline measurements include a baseline measurement of headache signs and/or symptoms, a baseline measurement of migraine symptoms and/or signs, a baseline measurement of chronic pain symptoms and/or signs, a baseline measurement of fibromyalgia symptoms and/or signs, a baseline measurement of chronic fatigue syndrome (ME) symptoms and/or signs, and a baseline measurement of motor neuron disease (e.g., ALS) symptoms and/or signs.

[00224] In some embodiments, the baseline measurement comprises a baseline CNS amyloid plaque accumulation measurement. Exemplary CNS amyloid plaque accumulation measurements may include a total amount of amyloid plaque in the CNS (e.g., the brain) and the concentration of amyloid plaque in an area of the CNS (e.g., the brain). CNS amyloid plaque accumulation may be measured in any appropriate manner, including, but not limited to a measurement of CNS amyloid plaque through the use of immunoprecipitation mass spectrometry, blood tests, cerebrospinal fluid tests, and a measurement of CNS amyloid plaque through the use of imaging (e.g., amyloid PET scan(s)).

[00225] In some embodiments, the baseline measurement comprises a baseline tau (e.g., CNS or CSF) accumulation. Exemplary tau (e.g., CNS or CSF) accumulation measurements may include a total amount of tau accumulation in the CNS (e.g., the brain or CSF), and the concentration of tau in an area of the CNS (e.g., the brain or CSF). Tau (e.g., CNS or CSF) accumulation may be measured in any appropriate manner, including, but not limited to imaging (e.g., tau PET scans), blood tests, and cerebrospinal fluid tests.

[00226] In some embodiments, the baseline measurement comprises a baseline CSF beta-amyloid 42 accumulation. Exemplary CSF beta-amyloid 42 accumulation measurements may include a total amount of beta-amyloid 42 accumulation in the CNS (e.g., the CSF), and the concentration of beta-amyloid 42 in an area of the CNS (e.g., CSF). CSF beta-amyloid 42 accumulation may be measured in any appropriate manner, including, but not limited to imaging (e.g., PET scans), blood tests, and cerebrospinal fluid tests.

[00227] In some embodiments, the baseline measurement comprises a baseline CSF beta-amyloid 42 accumulation. Exemplary CSF beta-amyloid 42 accumulation measurements may include a total amount

of beta-amyloid 42 accumulation in the CNS (e.g., the CSF), and the concentration of beta-amyloid 4 in an area of the CNS (e.g., CSF). CSF beta-amyloid 4 accumulation may be measured in any appropriate manner, including, but not limited to imaging (e.g., PET scans), blood tests, and cerebrospinal fluid tests.

[00228] In some embodiments, the baseline measurement comprises a baseline (e.g., CSF) phospho-tau accumulation. Exemplary (e.g., CSF) phospho-tau (e.g., 181) accumulation measurements may include a total amount of phospho-tau accumulation in the CNS (e.g., the CSF or the brain), and the concentration of (e.g., CSF) phospho-tau in an area of the CNS (e.g., CSF or the brain). Phospho-tau (e.g., CSF phospho-tau) accumulation may be measured in any appropriate manner, including, but not limited to imaging (e.g., PET scans), blood tests, and cerebrospinal fluid tests.

[00229] In some embodiments, the baseline measurement comprises a baseline Lewy body accumulation. Exemplary Lewy body accumulation measurements may include a total amount of Lewy body accumulation in the CNS (e.g., the brain), and the concentration of Lewy body in an area of the CNS (e.g., brain). Lewy body accumulation may be measured in any appropriate manner, including, but not limited to imaging (e.g., PET scan, MRI, CT scan, fluorodeoxyglucose PET scan, or single-photon emission computerized tomography (SPECT)), blood tests, and cerebrospinal fluid tests.

[00230] In some embodiments, the baseline measurement comprises a baseline (e.g., CSF) alpha-synuclein accumulation. Exemplary (e.g., CSF) alpha-synuclein accumulation measurements may include a total amount of alpha-synuclein accumulation in the CNS (e.g., the CSF or the brain), and the concentration of (e.g., CSF) alpha-synuclein in an area of the CNS (e.g., CSF or the brain). Alpha-synuclein (e.g., CSF alpha-synuclein) accumulation may be measured in any appropriate manner, including, but not limited to imaging (e.g., PET scans), blood tests, cerebrospinal fluid tests, and biopsy tests (e.g., Syn-One test).

[00231] In some embodiments, the baseline measurement is a baseline cognitive function measurement. The baseline cognitive function measurement may be obtained directly from the subject. For example, the subject may be administered a test. The test may include a cognitive test such as the Montreal Cognitive Assessment (MoCA), Mini-Mental State Exam (MMSE), or Mini-Cog. The test may include assessment of basic cognitive functions such as memory, language, executive frontal lobe function, apraxia, visuospatial ability, behavior, mood, orientation, or attention. The baseline cognitive function measurement may include a score. The baseline cognitive function measurement may be indicative of mild cognitive impairment, or of severe cognitive impairment. The baseline cognitive function measurement may be indicative of a neurological disorder.

[00232] In some embodiments, the baseline measurement is a baseline amyloid plaque measurement. The baseline amyloid plaque measurement may include a central nervous system (CNS) amyloid plaque measurement. In some embodiments, the baseline amyloid plaque measurement includes a baseline concentration or amount. The baseline amyloid plaque measurement may be performed using an imaging device. The imaging device may include a positron emission tomography (PET) device. The baseline amyloid plaque measurement may be performed on a biopsy. The baseline amyloid plaque measurement may be performed using a spinal tap (for example, when the baseline amyloid plaque measurement

includes a baseline cerebrospinal fluid (CSF) amyloid plaque measurement). In some embodiments, the baseline amyloid plaque measurement is obtained by an assay such as an immunoassay. The baseline beta amyloid plaque measurement may be indicative of a neurodegenerative disease such as Alzheimer's disease.

[00233] In some embodiments, the baseline measurement is a baseline beta-amyloid 42 measurement. The baseline beta-amyloid 42 measurement may include a cerebrospinal fluid (CSF) beta-amyloid 42 measurement. In some embodiments, the baseline beta-amyloid 42 measurement includes a baseline concentration or amount. The baseline beta-amyloid 42 measurement may be performed on a biopsy. The baseline beta-amyloid 42 measurement may be performed using a spinal tap (for example, when the baseline beta-amyloid 42 measurement includes a baseline CSF beta-amyloid 42 measurement). In some embodiments, the baseline beta-amyloid 42 measurement is obtained by an assay such as an immunoassay. The baseline beta-amyloid 42 measurement may be indicative of a neurodegenerative disease such as Alzheimer's disease.

[00234] In some embodiments, the baseline measurement is a baseline tau measurement. In some embodiments, the baseline tau measurement includes a baseline concentration or amount. The baseline tau measurement may be performed on a biopsy. In some embodiments, the baseline tau measurement is obtained by an assay such as an immunoassay. The baseline tau measurement may be indicative of a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00235] In some embodiments, the baseline tau measurement is a baseline central nervous system (CNS) tau measurement. The baseline tau measurement may include a baseline total tau measurement. The baseline tau measurement may include a baseline unphosphorylated tau measurement. The baseline tau measurement may include a baseline phosphorylated tau (phospho-tau) measurement. In some embodiments, the baseline tau measurement is a baseline tau accumulation measurement. In some embodiments, the baseline tau measurement is a baseline CNS tau accumulation measurement. The baseline CNS tau accumulation measurement may be indicative of a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00236] The baseline tau measurement may include a cerebrospinal fluid (CSF) tau measurement. The baseline CSF tau measurement may be performed after use of a spinal tap. The baseline CSF tau measurement may be indicative of a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00237] The baseline CSF tau measurement may include a baseline CSF phospho-tau measurement. The baseline CSF phospho-tau measurement may include an amount of phospho-tau in relation to total tau or unphosphorylated tau. For example, the baseline CSF phospho-tau measurement may include a phospho-tau/tau ratio. The baseline CSF phospho-tau measurement may be indicative of a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00238] In some embodiments, the baseline measurement is a baseline Lewy body measurement. The baseline Lewy body measurement may include a central nervous system (CNS) Lewy body measurement. In some embodiments, the baseline Lewy body measurement includes a baseline concentration or amount.

The baseline Lewy body measurement may be performed using an imaging device. The imaging device may include a positron emission tomography (PET) device. The baseline beta Lewy body measurement may be indicative of dementia.

[00239] In some embodiments, the baseline measurement is a baseline alpha-synuclein measurement. The baseline alpha-synuclein measurement may include a cerebrospinal fluid (CSF) alpha-synuclein measurement. In some embodiments, the baseline alpha-synuclein measurement includes a baseline concentration or amount. The baseline alpha-synuclein measurement may be performed on a biopsy. The baseline alpha-synuclein measurement may be performed using a spinal tap (for example, when the baseline alpha-synuclein measurement includes a baseline CSF alpha-synuclein measurement). In some embodiments, the baseline alpha-synuclein measurement is obtained by an assay such as an immunoassay. The baseline alpha-synuclein measurement may be indicative of a neurodegenerative disease such as Parkinson's disease. The baseline alpha-synuclein measurement may be indicative of dementia.

[00240] In some embodiments, the baseline measurement is a baseline headache measurement. In some embodiments, the baseline headache measurement is a baseline headache sign or symptom measurement. In some embodiments, the baseline headache measurement is a baseline migraine (e.g., with aura or without aura) measurement. In some embodiments, the baseline headache measurement is a frequency of a headache sign or symptom measurement. In some embodiments, the baseline headache measurement is a severity of a headache sign or symptom measurement. In some embodiments, the baseline headache measurement is a number of headache signs or symptoms. Exemplary signs and symptoms of headaches include pain (e.g., deep and constant) in the cheekbones, forehead, bridge of the nose, the cranium, or the back of the neck, aura, photophobia, phonophobia, and emesis.

[00241] In some embodiments, the baseline measurement is a baseline chronic pain measurement. In some embodiments, baseline chronic pain measurement is a baseline fibromyalgia measurement. In some embodiments, the baseline chronic pain measurement is a baseline chronic pain sign or symptom measurement. In some embodiments, the baseline chronic pain measurement is a frequency of a chronic pain sign or symptom measurement. In some embodiments, the baseline chronic pain measurement is a severity of a chronic pain sign or symptom measurement. In some embodiments, the baseline chronic pain measurement is a number of chronic pain signs or symptoms. Exemplary signs and symptoms of fibromyalgia include muscular pain, fatigue, depression, anxiety, sleeplessness, headache, and difficulty concentrating. Exemplary chronic pain disorders include postsurgical pain, post-trauma pain, low back pain, cancer pain, arthritis pain, muscular pain, and neuropathic pain (e.g., diabetic neuropathy).

[00242] In some embodiments, the baseline measurement is a baseline chronic fatigue syndrome (also referred to as myalgic encephalomyelitis) measurement. In some embodiments, the baseline chronic fatigue syndrome measurement is a baseline chronic fatigue syndrome sign or symptom measurement. In some embodiments, the baseline chronic fatigue syndrome measurement is a frequency of a headache sign or symptom measurement. In some embodiments, the baseline chronic fatigue syndrome measurement is a severity of a chronic fatigue syndrome sign or symptom measurement. In some embodiments, the baseline chronic fatigue syndrome measurement is a number of chronic fatigue syndrome signs or symptoms.

Exemplary signs and symptoms of chronic fatigue syndrome include extreme fatigue that lasts for extended periods of time (e.g., for at least six months) that cannot be fully explained by an underlying medical condition, fatigue that worsens with physical or mental activity, pain (e.g., joint or muscular), malaise, forgetfulness, anxiety, and depression.

[00243] In some embodiments, the baseline measurement is a baseline motor neuron disease measurement. In some embodiments, the baseline motor neuron disease measurement is an amyotrophic lateral sclerosis (ALS) measurement. In some embodiments, the baseline motor neuron disease measurement is a baseline motor neuron disease sign or symptom measurement. In some embodiments, the baseline motor neuron disease measurement is a frequency of a motor neuron disease sign or symptom measurement. In some embodiments, the baseline motor neuron disease measurement is a severity of a motor neuron disease sign or symptom measurement. In some embodiments, the baseline motor neuron disease measurement is a number of motor neuron disease signs or symptoms. Exemplary forms of motor neuron diseases include progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), ALS, and primary lateral sclerosis (PLS). Exemplary signs and symptoms of motor neuron diseases include motor control difficulties (e.g., difficulty walking or completing normal daily activities), muscular weakness, slurred speech, difficulty swallowing, and muscle cramps and twitching (e.g., in the arms, shoulders, or tongue).

[00244] In some embodiments, the baseline measurement is a baseline level of fibrinogen. In some embodiments, the baseline measurement is a baseline level of circulating fibrinogen.

[00245] In some embodiments, the baseline measurement is a baseline clotting or coagulation measurement. In some embodiments, the baseline measurement is a baseline clotting time measurement. In some embodiments, the baseline measurement is a baseline prothrombin time (PT). In some embodiments, the baseline measurement is a baseline International Normalized Ratio (INR). In some embodiments, the baseline measurement is a baseline activated partial thromboplastin time (aPTT).

[00246] In some cases, the disorder (e.g., baseline measurement) may be diagnosed or measured with the use of a questionnaire or a scoring system. In some cases, the disorder is diagnosed according to DSM-5 criteria. In some cases, the disorder is diagnosed by a healthcare professional (e.g., physician or the like).

[00247] Baseline measurements may include a baseline FGG protein measurement, or a baseline FGG mRNA measurement.

[00248] Baseline measurements may include any one or more of the baseline measurements disclosed herein.

[00249] In some embodiments, the baseline measurement is obtained directly from the subject. In some embodiments, the baseline measurement is obtained by observation, for example by observation of the subject or of the subject's tissue. In some embodiments, the baseline measurement is obtained noninvasively using an imaging device. In some embodiments, the baseline measurement is obtained invasively using an imaging device.

[00250] In some embodiments, the baseline measurement is obtained in a sample from the subject. In some embodiments, the baseline measurement is obtained in one or more histological tissue sections. In some embodiments, the baseline measurement is obtained by performing an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay, on the sample obtained from the subject. In some embodiments, the baseline measurement is obtained by an immunoassay, a colorimetric assay, a fluorescence assay, or a chromatography (e.g. HPLC) assay. In some embodiments, the baseline measurement is obtained by PCR.

[00251] In some embodiments, the baseline measurement is a baseline FGG protein measurement. In some embodiments, the baseline FGG protein measurement comprises a baseline FGG protein level. In some embodiments, the baseline FGG protein level is indicated as a mass or percentage of FGG protein per sample weight. In some embodiments, the baseline FGG protein level is indicated as a mass or percentage of FGG protein per sample volume. In some embodiments, the baseline FGG protein level is indicated as a mass or percentage of FGG protein per total protein within the sample. In some embodiments, the baseline FGG protein measurement is a baseline tissue FGG protein measurement. In some embodiments, the baseline FGG protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline FGG protein level is measured in the whole body. In some embodiments, the baseline FGG protein level is measured in the brain. In some embodiments, the baseline FGG protein level is measured in the liver. In some embodiments, the baseline FGG protein level is measured in the blood.

[00252] In some embodiments, the baseline measurement is a baseline FGG mRNA measurement. In some embodiments, the baseline FGG mRNA measurement comprises a baseline FGG mRNA level. In some embodiments, the baseline FGG mRNA level is measured in the liver. In some embodiments, the baseline FGG mRNA level is indicated as an amount or percentage of FGG mRNA per sample weight. In some embodiments, the baseline FGG mRNA level is indicated as an amount or percentage of FGG mRNA per sample volume. In some embodiments, the baseline FGG mRNA level is indicated as an amount or percentage of FGG mRNA per total mRNA within the sample. In some embodiments, the baseline FGG mRNA level is indicated as an amount or percentage of FGG mRNA per total nucleic acids within the sample. In some embodiments, the baseline FGG mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the baseline FGG mRNA measurement is a baseline tissue FGG mRNA measurement. In some embodiments, the baseline FGG mRNA measurement is obtained by an assay such as a polymerase chain reaction (PCR) assay. In some embodiments, the PCR comprises quantitative PCR (qPCR). In some embodiments, the PCR comprises reverse transcription of the FGG mRNA.

[00253] Some embodiments of the methods described herein include obtaining a sample from a subject. In some embodiments, the baseline measurement is obtained in a sample obtained from the subject. In some embodiments, the sample is obtained from the subject prior to administration or treatment of the subject with a composition described herein. In some embodiments, a baseline measurement is obtained in a sample obtained from the subject prior to administering the composition to

the subject. In some embodiments, the sample is obtained from the subject in a fasted state. In some embodiments, the sample is obtained from the subject after an overnight fasting period. In some embodiments, the sample is obtained from the subject in a fed state.

[00254] In some embodiments, the sample comprises a fluid. In some embodiments, the sample is a fluid sample. In some embodiments, the sample is a blood, plasma, or serum sample. In some embodiments, the sample comprises blood. In some embodiments, the sample is a blood sample. In some embodiments, the sample is a whole-blood sample. In some embodiments, the blood is fractionated or centrifuged. In some embodiments, the sample comprises plasma. In some embodiments, the sample is a plasma sample. A blood sample may be a plasma sample. In some embodiments, the sample comprises serum. In some embodiments, the sample is a serum sample. A blood sample may be a serum sample. In some embodiments, the sample is a CSF sample. In some embodiments the sample includes a CSF sample. In some embodiments, the sample is a CNS sample. In some embodiments the sample includes a CNS sample.

[00255] In some embodiments, the sample comprises a tissue. In some embodiments, the sample is a tissue sample. In some embodiments, the tissue comprises liver or brain tissue. For example, the baseline FGG mRNA measurement, or the baseline FGG protein measurement, may be obtained in a brain or liver sample obtained from the patient. In some embodiments, the tissue comprises neural tissue. In some embodiments, the tissue comprises neuronal tissue. In some embodiments, the tissue comprises neurons. In some embodiments, the tissue comprises glial cells. In some embodiments, the tissue comprises epithelial cells. In some embodiments, the tissue comprises liver tissue. The liver may include hepatocytes. In some embodiments, the tissue comprises brain tissue. In some embodiments, the sample comprises CSF fluid.

[00256] In some embodiments, the sample includes cells. In some embodiments, the sample comprises a cell. In some embodiments, the cell comprises a liver cell (e.g., hepatocyte), or a brain cell. In some embodiments, the cell is a liver cell. In some embodiments, the liver cell is a hepatocyte. In some embodiments, the cell is a brain cell. In some embodiments, the cell is a neuron. In some embodiments, the cell is a glial cell. In some embodiments, the cell is an epithelial cell. In some embodiments, the cell is a vasculature cell.

D. Effects

[00257] In some embodiments, the composition or administration of the composition affects a measurement such as mental disorder (e.g., psychiatric disorder or neurological disorder) measurement. In some embodiments, the composition or administration of the composition affects a measurement such as psychiatric measurement (e.g., a Montgomery-Asberg Depression Rating Scale (MADRS) score, a Hamilton Depression Rating Scale (HDRS) score, anxiety signs or symptoms, eating disorder signs or symptoms, substance-use disorder signs or symptoms, post-traumatic stress disorder (PTSD) signs or symptoms, bipolar disorder signs or symptoms, schizophrenia signs or symptoms, or psychosis signs or symptoms). In some embodiments, the composition or administration of the composition affects a measurement, such as psychiatric measurement, relative to the baseline measurement. In some

embodiments, administration of the composition affects a measurement of an aspect in any of **Tables 1A-1C and 2A-2B**. The measurement may include a fibrinogen measurement, a FGG mRNA measurement, or a FGG protein measurement. The measurement may include a clotting measurement, a prothrombin time (PT) measurement, an International Normalized Ratio (INR) measurement, or a activated partial thromboplastin time (aPTT) measurement.

[00258] In some embodiments, the composition or administration of the composition affects a measurement such as neurological measurement (e.g., decreased cognitive function, CNS amyloid plaques (e.g., accumulation), CNS tau accumulation, CSF beta-amyloid 42 (e.g., accumulation), CSF tau (e.g., accumulation), CSF phospho-tau (e.g., accumulation), Lewy bodies (e.g., accumulation), CSF alpha-synuclein (e.g., accumulation), headache signs or symptoms, migraine signs or symptoms, chronic pain signs or symptoms, fibromyalgia signs or symptoms, chronic fatigue (ME) signs or symptoms, motor neuron disease signs or symptoms, or ALS signs or symptoms). In some embodiments, the composition or administration of the composition affects a measurement, such as neurological measurement, relative to the baseline measurement.

[00259] In some embodiments, the measurement indicates that the disorder has been treated. In some embodiments, the measurement indicates that the severity of the disorder has decreased. In some embodiments, the measurement indicates that the severity of a sign or symptom of the disorder has decreased. In some embodiments, the measurement indicates that the frequency of a sign or symptom of the disorder has decreased.

[00260] Some embodiments of the methods described herein include obtaining the measurement from a subject. For example, the measurement may be obtained from the subject after treating the subject. In some embodiments, the measurement is obtained in a second sample (such as a fluid or tissue sample described herein) obtained from the subject after the composition is administered to the subject. In some embodiments, the measurement is an indication that the disorder has been treated.

[00261] In some embodiments, the measurement is obtained directly from the subject. In some embodiments, the measurement is obtained noninvasively using an imaging device. In some embodiments, the measurement is obtained in a second sample from the subject. In some embodiments, the measurement is obtained in one or more histological tissue sections. In some embodiments, the measurement is obtained by performing an assay on the second sample obtained from the subject. In some embodiments, the measurement is obtained by an assay, such as an assay described herein. In some embodiments, the assay is an immunoassay, a colorimetric assay, a fluorescence assay, a chromatography (e.g. HPLC) assay, or a PCR assay. In some embodiments, the measurement is obtained by an assay such as an immunoassay, a colorimetric assay, a fluorescence assay, or a chromatography (e.g. HPLC) assay. In some embodiments, the measurement is obtained by PCR. In some embodiments, the measurement is obtained by histology. In some embodiments, the measurement is obtained by observation. In some embodiments, additional measurements are made, such as in a 3rd sample, a 4th sample, or a fifth sample.

[00262] In some embodiments, the measurement is obtained within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, within 6 hours, within 12 hours, within 18 hours, or within 24 hours

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

[00263] In some embodiments, the composition reduces the measurement relative to the baseline measurement. For example, an adverse phenotype of a psychiatric or neurological disorder may be reduced upon administration of the composition. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline measurement. In some embodiments, the measurement is decreased by about 10% or more, relative to the baseline measurement. In some embodiments, the measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline measurement. In some embodiments, the measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline measurement. In some embodiments, the measurement is decreased by no more than about 10%, relative to the baseline measurement. In some embodiments, the measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline measurement. In some embodiments, the measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00264] In some embodiments, the composition increases the measurement relative to the baseline measurement. For example, a protective psychiatric or neurological phenotype may be increased upon administration of the composition. In some embodiments, the increase is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the increase is measured directly in the subject after administering the composition to the subject. In some embodiments, the measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline measurement. In some embodiments, the measurement is increased by about

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

[00265] In some embodiments, the measurement is a Montgomery-Asberg Depression Rating Scale (MADRS) score. In some embodiments, the MADRS score comprises a numerical value such as a number of points. In some embodiments, the numerical value is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60, or a range defined by any two of the aforementioned numerical values. In some embodiments, the numerical value is 0. In some embodiments, the numerical value is 1-5. In some embodiments, the numerical value is 6-10. In some embodiments, the numerical value is 11-15. In some embodiments, the numerical value is 16-20. In some embodiments, the numerical value is 21-25. In some embodiments, the numerical value is 26-30. In some embodiments, the numerical value is 31-35. In some embodiments, the numerical value is 36-40. In some embodiments, the numerical value is 41-45. In some embodiments, the numerical value is 46-50. In some embodiments, the numerical value is 51-55. In some embodiments, the numerical value is 56-60. In some embodiments, the numerical value is 0-60. In some embodiments, the MADRS score comprises a subscore such as a apparent sadness score, a reported sadness score, a inner tension score, a reduced sleep score, a reduced appetite score, a concentration difficulties score, a lassitude score, a inability to feel score, a pessimistic thoughts score, or a suicidal thoughts score. Each subscore may comprise a numerical value of 0, 1, 2, 3, 4, 5, or 6, or a range of such numerical values. In some embodiments, the MADRS score comprises a numerical value below a threshold numerical value that is indicative of a depressive disorder. In some embodiments, the subscore comprises a numerical value below a threshold numerical value that is indicative of a depressive disorder.

[00266] In some embodiments, the composition reduces the MADRS score relative to the baseline MADRS score. In some embodiments, the reduced MADRS score by observing and/or questioning the subject after administering the composition to the subject. In some embodiments, the MADRS score is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by about 10% or more, relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by no more than about 10%, relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages. In some embodiments, the MADRS score is decreased by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 points, relative to the baseline MADRS score, or by a range of points defined by any two of the aforementioned numbers of points relative to the baseline MADRS score. In some embodiments, the MADRS score is decreased by 1-5 points. In some embodiments, the MADRS score is decreased by 6-10 points. In some embodiments, the MADRS score is decreased by 11-15 points. In some embodiments, the MADRS score is decreased by 16-20 points. In some embodiments, the MADRS score is decreased by 21-25 points. In some embodiments, the MADRS score is decreased by 26-30 points. In some embodiments, the MADRS score is decreased by 31-35 points. In some embodiments, the MADRS score is decreased by 36-40 points. In some embodiments, the MADRS score is decreased by 41-45 points. In some embodiments, the MADRS score is decreased by 46-50 points. In some embodiments, the MADRS score is decreased by 51-55 points. In some embodiments, the MADRS score is decreased by 56-60 points.

[00267] In some embodiments, following treatment with the oligonucleotide, the MADRS score of the subject is decreased such that the MADRS score of the subject changes from severe depression to mild or moderate depression, or to normal non-depressed symptomology. For example, the MADRS score of the subject may be below 35 following treatment. In some embodiments, the MADRS score changes from moderate depression to mild depression, or to normal non-depressed symptomology. For example, the MADRS score of the subject may be below 20 following treatment. In some embodiments, the MADRS score changes from mild depression to normal non-depressed symptomology. For example, the MADRS score of the subject may be below 7 following treatment.

[00268] In some embodiments, the measurement is a Hamilton Depression Rating Scale (HDRS) score. In some embodiments, the HDRS score comprises a numerical value such as a number of points. In some embodiments, the numerical value is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, or a range defined by any two of the aforementioned numerical values. In some embodiments, the numerical value is 0. In some embodiments, the numerical value is 1-5. In some embodiments, the numerical value is 6-10. In some embodiments, the numerical value is 11-15. In some embodiments, the numerical value is 16-20. In some embodiments, the numerical value is 21-25. In some embodiments, the numerical value is 26-30. In some embodiments, the numerical value is 31-35. In some embodiments, the numerical value is 36-40. In some embodiments, the numerical value is 41-45. In some embodiments, the numerical value is 46-50. In some embodiments, the numerical value is 0-50. In some embodiments, the HDRS score comprises a subscore such as a depressed mood score, a feelings of guilt score, a suicide score, a insomnia early in the night score, a insomnia in the middle of the night score, a insomnia in early hours of the morning score, a work and activities score, a retardation score, a agitation score, an anxiety psychic score, an anxiety somatic score, a somatic symptoms of gastrointestinal score, a general somatic score, a genital symptoms score, a hypochondriasis score, a loss of weight score, or a insight score. Subscores may comprise a numerical value of 0, 1, or 2, or a range of such numerical values. Subscores may comprise a numerical value of 0, 1, 2, 3, or 4, or a range of such numerical values. In some embodiments, the HDRS score comprises a numerical value below a threshold numerical value that is indicative of a depressive disorder. For example, a score of below 20 may indicate a lack of moderate or severe depression. In some embodiments, the subscore comprises a numerical value below a threshold numerical value that is indicative of the depressive disorder.

[00269] In some embodiments, the composition reduces the HDRS score relative to the baseline HDRS score. In some embodiments, the reduced HDRS score by observing and/or questioning the subject after administering the composition to the subject. In some embodiments, the HDRS score is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by about 10% or more, relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by no more than about 10%, relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages. In some embodiments, the HDRS score is

decreased by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 points, relative to the baseline HDRS score, or by a range of points defined by any two of the aforementioned numbers of points relative to the baseline HDRS score. In some embodiments, the HDRS score is decreased by 1-5 points. In some embodiments, the HDRS score is decreased by 6-10 points. In some embodiments, the HDRS score is decreased by 11-15 points. In some embodiments, the HDRS score is decreased by 16-20 points. In some embodiments, the HDRS score is decreased by 21-25 points. In some embodiments, the HDRS score is decreased by 26-30 points. In some embodiments, the HDRS score is decreased by 31-35 points. In some embodiments, the HDRS score is decreased by 36-40 points. In some embodiments, the HDRS score is decreased by 41-45 points. In some embodiments, the HDRS score is decreased by 46-50 points. In some embodiments, the HDRS score is decreased by 51-55 points. In some embodiments, the HDRS score is decreased by 56-60 points.

[00270] In some embodiments, following treatment with the oligonucleotide, the HDRS score of the subject is decreased such that the HDRS score of the subject changes from severe depression to mild or moderate depression, or to normal non-depressed symptomology. In some embodiments, the HDRS score changes from moderate depression to mild depression, or to normal non-depressed symptomology. For example, the HDRS score of the subject may be below 20 following treatment. In some embodiments, the HDRS score changes from mild depression to normal non-depressed symptomology. For example, the HDRS score of the subject may be below 8 following treatment.

[00271] In some embodiments, the measurement is an anxiety measurement. The anxiety measurement may include an assessment of a symptom of anxiety. In some embodiments, the symptom of anxiety includes stress, worry, or restlessness. In some cases, the symptom of anxiety includes one or more behavioral symptoms such as hypervigilance, irritability, or restlessness. In some cases, the symptom of anxiety includes one or more cognitive symptoms such as lack of concentration, racing thoughts, or unwanted thoughts. In some cases, the symptom of anxiety includes one or more whole body symptoms such as fatigue or sweating. In some cases, the symptoms of anxiety include any of excessive worry, fear, feeling of impending doom, insomnia, nausea, palpitations, or trembling. In some embodiments, the symptom includes one or more panic attacks. The anxiety measurement may include a questionnaire or assessment. The assessment may include an amount, frequency, duration, or intensity of the anxiety or symptoms of anxiety. The anxiety measurement may include an amount of time since feeling anxious or since feeling symptoms of anxiety. The anxiety measurement may include a frequency of feeling anxious or feeling symptoms of anxiety. In some embodiments, the composition reduces the anxiety measurement relative to the baseline anxiety measurement. For example, the composition may reduce the anxiety measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00272] In some embodiments, the measurement is an eating disorder measurement. Examples of eating disorders include anorexia, bulimia, binge eating disorder, pica, rumination, or avoidant eating disorder. In some embodiments, the eating disorder includes anorexia nervosa. In some embodiments, the

eating disorder includes bulimia. In some embodiments, the eating disorder includes binge eating. In some embodiments, the eating disorder includes pica. The eating disorder measurement may include an assessment of a symptom of eating disorder. Some examples of symptoms of an eating disorder comprising anorexia nervosa include being considerably underweight compared with people of similar age and height, very restricted eating patterns, an intense fear of gaining weight or persistent behaviors to avoid gaining weight despite being underweight, a relentless pursuit of thinness and unwillingness to maintain a healthy weight, a heavy influence of body weight or perceived body shape on self-esteem, a distorted body image, or denial of being seriously underweight. The eating disorder measurement may include a questionnaire or assessment. The assessment may include an amount, frequency, duration, or intensity of the eating disorder or symptoms. The eating disorder measurement may include an amount of time since engaging in the eating disorder (e.g. binding, purging, or starving). The eating disorder measurement may include a frequency of engaging in the eating disorder. In some embodiments, the composition reduces the eating disorder measurement relative to the baseline eating disorder measurement. For example, the composition may reduce the eating disorder measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00273] In some embodiments, the measurement is a substance-use measurement. In some embodiments, the substance-use measurement includes a determination of a level of addiction to an addictive substance. Examples of addictive substances include alcohol, antianxiety drugs, sedative drugs, caffeine, cannabis (e.g. including marijuana or synthetic cannabinoids), hallucinogens (e.g. LSD, phencyclidine, or psilocybin), inhalants (e.g. paint thinner or some glues), opioids (e.g. fentanyl, morphine, or oxycodone), stimulants (e.g. amphetamines or cocaine), tobacco, or anabolic steroids. The substance abuse measurement may include an amount of time since engaging in the substance-use disorder or experiencing symptoms of the substance-use disorder. The substance abuse measurement may include a frequency of engaging in the substance-use disorder or experiencing symptoms of the substance-use disorder. The determination of a level of addiction to an addictive substance may include a questionnaire or assessment. The substance abuse measurement or the assessment may include an amount, frequency, duration, or intensity of the substance-use disorder or symptoms. The determination of a level of addiction to an addictive substance may include an amount of time since ingesting the addictive substance. The determination of a level of addiction to an addictive substance may include a frequency of ingesting the addictive substance. In some embodiments, the composition reduces the substance abuse measurement relative to the baseline substance abuse measurement. For example, the composition may reduce the substance abuse measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00274] In some embodiments, the measurement is a PTSD measurement. In some embodiments, the PTSD measurement includes a determination of the level of severity of PTSD. The assessment of a sign or symptom of PTSD may include the number of signs or symptoms of PTSD. The determination of the level of severity of PTSD may include the time since last experiencing a PTSD flashback (e.g., reliving the

traumatic event as if it were happening again), nightmare, or severe anxiety. The assessment may include a frequency in PTSD related flashbacks, nightmares, or severe anxiety episodes. The assessment may include a severity of a sign or symptom of PTSD. The assessment may include a frequency of a sign or symptom of PTSD. Exemplary signs and symptoms of PTSD may include intrusive memories (e.g., recurrent, unwanted distressing memories of a traumatic event, severe emotional distress or physical reactions to something that reminiscent of the traumatic event, attempts to avoid thinking or talking about the traumatic event, avoiding places, activities or people reminiscent of the traumatic event, thoughts of hopelessness, memory problems, difficulty maintaining close relationships, and feeling a lack of interest in activities that were once enjoyed. In some embodiments, the composition reduces the PTSD measurement relative to the baseline substance abuse measurement. For example, the composition may reduce the PTSD measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00275] In some embodiments, the measurement is a bipolar disorder measurement. In some embodiments, the bipolar disorder measurement is a sign or symptom of bipolar disorder. The assessment of a sign or symptom of bipolar disorder may include a frequency of a sign or symptom of bipolar disorder. The assessment of a sign or symptom of bipolar disorder may include a severity of a sign or symptom of bipolar disorder. The assessment of a sign or symptom of bipolar disorder may include the number of signs or symptoms of bipolar disorder. Exemplary signs and symptoms of bipolar disorder include any of the bipolar signs and symptoms disclosed herein, including, manic episodes (e.g., experiencing feelings of increased activity, energy, or agitation, an exaggerated sense of well-being and self-confidence, a decreased need for sleep, racing thoughts, distractibility, and a decreased ability to control impulses), and major depressive episodes (e.g., experiencing a depressed mood, marked loss of interest of feelings of pleasure, fatigue or loss of energy, feelings of guilt or worthlessness, and a decreased ability to think or concentrate). In some embodiments, the composition reduces the bipolar disorder measurement relative to the baseline substance abuse measurement. For example, the composition may reduce the bipolar disorder measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00276] In some embodiments, the measurement comprises a schizophrenia measurement. In some embodiments, the schizophrenia measurement is a sign or symptom of schizophrenia. The assessment of a sign or symptom of schizophrenia may include a frequency of a sign or symptom of schizophrenia. The assessment of a sign or symptom of schizophrenia may include a severity of a sign or symptom of schizophrenia. The assessment of a sign or symptom of schizophrenia may include the number of signs or symptoms of schizophrenia. Exemplary signs and symptoms of schizophrenia may include delusions, hallucinations, disorganized thoughts and speech, disorganized or abnormal motor behavior, and negative symptoms (e.g., social withdrawal, anhedonia, avolition, decreased sense of purpose, lack of interest in activities, flat affect, lack of eye contact, and physical inactivity. In some embodiments, the composition reduces the schizophrenia measurement relative to the baseline substance abuse measurement. For

example, the composition may reduce the schizophrenia measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00277] In some embodiments, the measurement comprises a psychosis measurement. In some embodiments, the psychosis measurement is a sign or symptom of psychosis. The assessment of a sign or symptom of psychosis may include a frequency of a sign or symptom of psychosis. The assessment of a sign or symptom of psychosis may include a severity of a sign or symptom of psychosis. The assessment of a sign or symptom of psychosis may include the number of signs or symptoms of psychosis. Exemplary signs and symptoms of psychosis may include difficulty concentrating, depressed mood, anxiety, excessive suspiciousness, delusions, and hallucinations. In some embodiments, the composition reduces the schizophrenia measurement relative to the baseline psychosis measurement. For example, the composition may reduce the psychosis measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00278] In some embodiments, the measurement comprises a measurement of a neurological disorder. Non-limiting examples of measurements of neurological disorders include a measurement of cognitive function, a measurement of CNS amyloid plaque(s) (e.g., accumulation), a measurement of CNS tau accumulation, a measurement of CSF beta-amyloid 42 (e.g., accumulation), a measurement of CSF tau (e.g., accumulation), a measurement of CSF phospho-tau (e.g., accumulation), a measurement of Lewy bodies (e.g., accumulation), or a measurement of CSF alpha-synuclein (e.g., accumulation). Further non-limiting examples of measurements include a measurement of headache signs and/or symptoms, a measurement of migraine symptoms and/or signs, a measurement of chronic pain symptoms and/or signs, a measurement of fibromyalgia symptoms and/or signs, a measurement of chronic fatigue syndrome (ME) symptoms and/or signs, and a measurement of motor neuron disease (e.g., ALS) symptoms and/or signs. In some embodiments, the composition reduces the neurological disorder measurement relative to the baseline neurological disorder measurement. For example, the composition may reduce the neurological disorder measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00279] In some embodiments, the measurement is a cognitive function measurement. The cognitive function measurement may be obtained directly from the subject. For example, the subject may be administered a test. The test may include a cognitive test such as the Montreal Cognitive Assessment (MoCA), Mini-Mental State Exam (MMSE), or Mini-Cog. The test may include assessment of basic cognitive functions such as memory, language, executive frontal lobe function, apraxia, visuospatial ability, behavior, mood, orientation, or attention. The cognitive function measurement may include a score. The cognitive function measurement may be indicative of a lack of cognitive impairment. In some embodiments, the cognitive function measurement is indicative of mild cognitive impairment, and the baseline cognitive function measurement is indicative of severe cognitive impairment. The cognitive function measurement may be indicative of a neurological disorder.

[00280] In some embodiments, the composition increases the cognitive function measurement relative to the baseline cognitive function measurement. In some embodiments, the increase is measured directly in the subject after administering the composition to the subject. In some embodiments, the cognitive function measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by about 10% or more, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by about 100% or more, increased by about 250% or more, increased by about 500% or more, increased by about 750% or more, or increased by about 1000% or more, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by no more than about 10%, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by no more than about 100%, increased by no more than about 250%, increased by no more than about 500%, increased by no more than about 750%, or increased by no more than about 1000%, relative to the baseline cognitive function measurement. In some embodiments, the cognitive function measurement is increased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 250%, 500%, 750%, or 1000%, or by a range defined by any of the two aforementioned percentages.

[00281] In some embodiments, the measurement is an amyloid plaque measurement. The amyloid plaque measurement may include a central nervous system (CNS) amyloid plaque measurement. In some embodiments, the amyloid plaque measurement includes a concentration or amount. The amyloid plaque measurement may be performed using an imaging device. The imaging device may include a positron emission tomography (PET) device. The amyloid plaque measurement may be performed on a biopsy. The amyloid plaque measurement may be performed using a spinal tap (for example, when the amyloid plaque measurement includes a cerebrospinal fluid (CSF) amyloid plaque measurement). In some embodiments, the amyloid plaque measurement is obtained by an assay such as an immunoassay. The beta amyloid plaque measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Alzheimer's disease.

[00282] In some embodiments, the composition reduces the amyloid plaque measurement relative to the baseline amyloid plaque measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some

embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the amyloid plaque measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline amyloid plaque measurement. In some embodiments, the amyloid plaque measurement is decreased by about 10% or more, relative to the baseline amyloid plaque measurement. In some embodiments, the amyloid plaque measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline amyloid plaque measurement. In some embodiments, the amyloid plaque measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline amyloid plaque measurement. In some embodiments, the amyloid plaque measurement is decreased by no more than about 10%, relative to the baseline amyloid plaque measurement. In some embodiments, the amyloid plaque measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline amyloid plaque measurement. In some embodiments, the amyloid plaque measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00283] In some embodiments, the measurement is a tau measurement. In some embodiments, the tau measurement includes a concentration or amount. The tau measurement may be performed on a biopsy. In some embodiments, the tau measurement is obtained by an assay such as an immunoassay. The beta tau measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00284] In some embodiments, the tau measurement is a central nervous system (CNS) tau measurement. The tau measurement may include a total tau measurement. The tau measurement may include a unphosphorylated tau measurement. The tau measurement may include a phosphorylated tau (phospho-tau) measurement. In some embodiments, the tau measurement is a tau accumulation measurement. In some embodiments, the tau measurement is a CNS tau accumulation measurement. The CNS tau accumulation measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00285] In some embodiments, the composition reduces the CNS tau accumulation measurement relative to the baseline CNS tau accumulation measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the CNS tau accumulation measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline CNS tau accumulation measurement. In some embodiments, the CNS tau accumulation measurement is decreased by about 10% or more, relative to the baseline CNS tau accumulation measurement. In some embodiments, the CNS tau accumulation measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the

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

[00286] The tau measurement may include a cerebrospinal fluid (CSF) tau measurement. The CSF tau measurement may be performed after use of a spinal tap. The CSF tau measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00287] In some embodiments, the composition reduces the CSF tau measurement relative to the baseline CSF tau measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured in a second CSF sample obtained from the subject after administering the composition to the subject. In some embodiments, the CSF tau measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline CSF tau measurement. In some embodiments, the CSF tau measurement is decreased by about 10% or more, relative to the baseline CSF tau measurement. In some embodiments, the CSF tau measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline CSF tau measurement. In some embodiments, the CSF tau measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline CSF tau measurement. In some embodiments, the CSF tau measurement is decreased by no more than about 10%, relative to the baseline CSF tau measurement. In some embodiments, the CSF tau measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline CSF tau measurement. In some embodiments, the CSF tau measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00288] The CSF tau measurement may include a CSF phospho-tau measurement. The CSF phospho-tau measurement may include an amount of phospho-tau in relation to total tau or unphosphorylated tau. For example, the CSF phospho-tau measurement may include a phospho-tau/tau ratio. The CSF phospho-

tau measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease.

[00289] In some embodiments, the composition reduces the CSF phospho-tau measurement relative to the baseline CSF phospho-tau measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured in a second CSF sample obtained from the subject after administering the composition to the subject. In some embodiments, the CSF phospho-tau measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline CSF phospho-tau measurement. In some embodiments, the CSF phospho-tau measurement is decreased by about 10% or more, relative to the baseline CSF phospho-tau measurement. In some embodiments, the CSF phospho-tau measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline CSF phospho-tau measurement. In some embodiments, the CSF phospho-tau measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline CSF phospho-tau measurement. In some embodiments, the CSF phospho-tau measurement is decreased by no more than about 10%, relative to the baseline CSF phospho-tau measurement. In some embodiments, the CSF phospho-tau measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline CSF phospho-tau measurement. In some embodiments, the CSF phospho-tau measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00290] In some embodiments, the measurement is a alpha-synuclein measurement. The alpha-synuclein measurement may include a cerebrospinal fluid (CSF) alpha-synuclein measurement. In some embodiments, the alpha-synuclein measurement includes a concentration or amount. The alpha-synuclein measurement may be performed on a biopsy. The alpha-synuclein measurement may be performed using a spinal tap (for example, when the alpha-synuclein measurement includes a CSF alpha-synuclein measurement). In some embodiments, the alpha-synuclein measurement is obtained by an assay such as an immunoassay. The alpha-synuclein measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Parkinson's disease. The alpha-synuclein measurement may be indicative of a treatment effect of the oligonucleotide on dementia.

[00291] In some embodiments, the composition reduces the alpha-synuclein measurement relative to the baseline alpha-synuclein measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the alpha-synuclein measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline alpha-synuclein measurement. In some embodiments, the alpha-synuclein measurement is decreased by about 10% or more, relative to the baseline alpha-synuclein measurement. In some embodiments, the alpha-synuclein measurement is decreased by about 20% or

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

[00292] In some embodiments, the measurement is a Lewy body measurement. The Lewy body measurement may include a central nervous system (CNS) Lewy body measurement. In some embodiments, the Lewy body measurement includes a concentration or amount. The Lewy body measurement may be performed using an imaging device. The imaging device may include a positron emission tomography (PET) device. The beta Lewy body measurement may be indicative of a treatment effect of the oligonucleotide on dementia.

[00293] In some embodiments, the composition reduces the Lewy body measurement relative to the baseline Lewy body measurement. In some embodiments, the reduction is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the Lewy body measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline Lewy body measurement. In some embodiments, the Lewy body measurement is decreased by about 10% or more, relative to the baseline Lewy body measurement. In some embodiments, the Lewy body measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline Lewy body measurement. In some embodiments, the Lewy body measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline Lewy body measurement. In some embodiments, the Lewy body measurement is decreased by no more than about 10%, relative to the baseline Lewy body measurement. In some embodiments, the Lewy body measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline Lewy body measurement. In some embodiments, the Lewy body measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00294] In some embodiments, the measurement is a beta-amyloid 42 measurement. The beta-amyloid 42 measurement may include a cerebrospinal fluid (CSF) beta-amyloid 42 measurement. In some embodiments, the beta-amyloid 42 measurement includes a concentration or amount. The beta-amyloid 42 measurement may be performed on a biopsy. The beta-amyloid 42 measurement may be performed using a spinal tap (for example, when the beta-amyloid 42 measurement includes a CSF beta-amyloid 42 measurement). In some embodiments, the beta-amyloid 42 measurement is obtained by an assay such as an immunoassay. The beta-amyloid 42 measurement may be indicative of a treatment effect of the oligonucleotide on a neurodegenerative disease such as Alzheimer's disease.

[00295] In some embodiments, the composition reduces the CSF beta-amyloid 42 measurement relative to the baseline beta-amyloid 42 measurement. In some embodiments, the reduction is measured in a second sample (for example, a CSF sample) obtained from the subject after administering the composition to the subject. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline CSF beta-amyloid 42 measurement. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by about 10% or more, relative to the baseline CSF beta-amyloid 42 measurement. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline CSF beta-amyloid 42 measurement. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline CSF beta-amyloid 42 measurement. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by no more than about 10%, relative to the baseline CSF beta-amyloid 42 measurement. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline CSF beta-amyloid 42 measurement. In some embodiments, the CSF beta-amyloid 42 measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00296] In some embodiments, the measurement is a headache measurement. In some embodiments, the headache measurement is a headache sign or symptom measurement. In some embodiments, the headache measurement is a migraine (e.g., with aura or without aura) measurement. In some embodiments, the headache measurement is a frequency of a headache sign or symptom measurement. In some embodiments, the headache measurement is a severity of a headache sign or symptom measurement. In some embodiments, the headache measurement is a number of headache signs or symptoms. Exemplary signs and symptoms of headaches include pain (e.g., deep and constant) in the cheekbones, forehead, bridge of the nose, the cranium, or the back of the neck, aura, photophobia, phonophobia, and emesis. In some embodiments, the composition reduces the headache measurement relative to the baseline headache measurement. For example, the composition may reduce the headache measurement by 2.5%, 5%, 7.5%,

10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00297] In some embodiments, the measurement is a chronic pain measurement. In some embodiments, chronic pain measurement is a fibromyalgia measurement. In some embodiments, the chronic pain measurement is a chronic pain sign or symptom measurement. In some embodiments, the chronic pain measurement is a frequency of a chronic pain sign or symptom measurement. In some embodiments, the chronic pain measurement is a severity of a chronic pain sign or symptom measurement. In some embodiments, the chronic pain measurement is a number of chronic pain signs or symptoms. Exemplary signs and symptoms of fibromyalgia include muscular pain, fatigues, depression, anxiety, sleeplessness, headache, and difficulty concentrating. Exemplary chronic pain disorders include postsurgical pain, post-trauma pain, low back pain, cancer pain, arthritis pain, muscular pain, and neuropathic pain (e.g., diabetic neuropathy). In some embodiments, the composition reduces the chronic pain (e.g., fibromyalgia) measurement relative to the baseline chronic pain (e.g., fibromyalgia) measurement. For example, the composition may reduce the chronic pain (e.g., fibromyalgia) measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00298] In some embodiments, the measurement is a chronic fatigue syndrome (also referred to as myalgic encephalomyelitis) measurement. In some embodiments, the chronic fatigue syndrome measurement is a chronic fatigue syndrome sign or symptom measurement. In some embodiments, the chronic fatigue syndrome measurement is a frequency of a headache sign or symptom measurement. In some embodiments, the chronic fatigue syndrome measurement is a severity of a chronic fatigue syndrome sign or symptom measurement. In some embodiments, the chronic fatigue syndrome measurement is a number of chronic fatigue syndrome signs or symptoms. Exemplary signs and symptoms of chronic fatigue syndrome include extreme fatigue that lasts for extended periods of time (e.g., for at least six months) that cannot be fully explained by an underlying medical condition, fatigue that worsens with physical or mental activity, pain (e.g., joint or muscular), malaise, forgetfulness, anxiety, and depression. In some embodiments, the composition reduces the chronic fatigue syndrome measurement relative to the baseline chronic fatigue syndrome measurement. For example, the composition may reduce the chronic fatigue syndrome measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00299] In some embodiments, the measurement is a motor neuron disease measurement. In some embodiments, the motor neuron disease measurement is an amyotrophic lateral sclerosis (ALS) measurement. In some embodiments, the motor neuron disease measurement is a motor neuron disease sign or symptom measurement. In some embodiments, the motor neuron disease measurement is a frequency of a motor neuron disease sign or symptom measurement. In some embodiments, the motor neuron disease measurement is a severity of a motor neuron disease sign or symptom measurement. In some embodiments, the motor neuron disease measurement is a number of motor neuron disease signs or

symptoms. Exemplary forms of motor neuron diseases include progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), ALS, and primary lateral sclerosis (PLS). Exemplary signs and symptoms of motor neuron diseases include motor control difficulties (e.g., difficulty walking or completing normal daily activities), muscular weakness, slurred speech, difficulty swallowing, and muscle cramps and twitching (e.g., in the arms, shoulders, or tongue). In some embodiments, the composition reduces the motor neuron disease (e.g., ALS) measurement relative to the baseline chronic fatigue syndrome measurement. For example, the composition may reduce the motor neuron disease (e.g., ALS) measurement by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00300] In some embodiments, the measurement is a fibrinogen measurement. In some embodiments, the measurement is a measurement of circulating fibrinogen. In some embodiments, the composition reduces the fibrinogen measurement relative to the baseline fibrinogen measurement. In some embodiments, the composition reduces the circulating fibrinogen measurement relative to the baseline circulating fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by about 10% or more, relative to the baseline fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by no more than about 10%, relative to the baseline fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline fibrinogen measurement. In some embodiments, the fibrinogen measurement is decreased by 2.5%, 5%, 7.5%, 19%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00301] In some embodiments, the measurement is a clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is a prothrombin time (PT). In some embodiments, the clotting or coagulation measurement is an International Normalized Ratio (INR). In some embodiments, the clotting or coagulation measurement is an activated partial thromboplastin time (aPTT). In some embodiments, the composition reduces the clotting or coagulation measurement relative to the baseline clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is increased by about 10% or more, relative to the baseline clotting or coagulation

measurement. In some embodiments, the clotting or coagulation measurement is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is increased by no more than about 10%, relative to the baseline clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline clotting or coagulation measurement. In some embodiments, the clotting or coagulation measurement is increased by 2.5%, 5%, 7.5%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages. In some embodiments, the clotting or coagulation measurement is increased by no more than about 20%, no more than about 40%, no more than about 80%, no more than about 100%, no more than about 120%, no more than about 140%, no more than about 160%, no more than about 180%, no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or more than about 1000% relative to the baseline clotting or coagulation measurement.

[00302] In some embodiments, the measurement is an FGG protein measurement. In some embodiments, the FGG protein measurement comprises an FGG protein level. In some embodiments, the FGG protein level is a FGG protein level in the whole body. In some embodiments, the FGG protein level is a FGG protein level in the blood. In some embodiments, the FGG protein level is a FGG protein level in the brain. In some embodiments, the FGG protein level is a FGG protein level in the liver. In some embodiments, the FGG protein level is indicated as a mass or percentage of FGG protein per sample weight. In some embodiments, the FGG protein level is indicated as a mass or percentage of FGG protein per sample volume. In some embodiments, the FGG protein level is indicated as a mass or percentage of FGG protein per total protein within the sample. In some embodiments, the FGG protein measurement is a circulating FGG protein measurement. In some embodiments, the FGG protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[00303] In some embodiments, the composition reduces the FGG protein measurement relative to the baseline FGG protein measurement. In some embodiments, the composition reduces circulating FGG protein levels relative to the baseline FGG protein measurement. In some embodiments, the composition reduces tissue (e.g. brain, liver, blood, or whole body) FGG protein levels relative to the baseline FGG protein measurement. In some embodiments, the reduced FGG protein levels are measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the FGG protein measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline FGG protein measurement. In some embodiments, the FGG

protein measurement is decreased by about 10% or more, relative to the baseline FGG protein measurement. In some embodiments, the FGG protein measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline FGG protein measurement. In some embodiments, the FGG protein measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline FGG protein measurement. In some embodiments, the FGG protein measurement is decreased by no more than about 10%, relative to the baseline FGG protein measurement. In some embodiments, the FGG protein measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline FGG protein measurement. In some embodiments, the FGG protein measurement is decreased by 2.5%, 5%, 7.5%, 19%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00304] In some embodiments, the measurement is an FGG mRNA measurement. In some embodiments, the FGG mRNA measurement comprises an FGG mRNA level. In some embodiments, the FGG mRNA level is measured in the liver. In some embodiments, the FGG mRNA level is indicated as an amount or percentage of FGG mRNA per sample weight. In some embodiments, the FGG mRNA level is indicated as an amount or percentage of FGG mRNA per sample volume. In some embodiments, the FGG mRNA level is indicated as an amount or percentage of FGG mRNA per total mRNA within the sample. In some embodiments, the FGG mRNA level is indicated as an amount or percentage of FGG mRNA per total nucleic acids within the sample. In some embodiments, the FGG mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the FGG mRNA measurement is obtained by an assay such as a PCR assay. In some embodiments, the PCR comprises qPCR. In some embodiments, the PCR comprises reverse transcription of the FGG mRNA.

[00305] In some embodiments, the composition reduces the FGG mRNA measurement relative to the baseline FGG mRNA measurement. In some embodiments, the FGG mRNA measurement is obtained in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the composition reduces FGG mRNA levels relative to the baseline FGG mRNA levels. In some embodiments, the reduced FGG mRNA levels are measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the second sample is a liver sample. In some embodiments, the FGG mRNA measurement is reduced by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline v mRNA measurement. In some embodiments, the FGG mRNA measurement is decreased by about 10% or more, relative to the baseline FGG mRNA measurement. In some embodiments, the FGG mRNA measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline FGG

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

III. DEFINITIONS

[00306] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[00307] Throughout this application, various embodiments may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[00308] As used in the specification and claims, the singular forms “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a sample” includes a plurality of samples, including mixtures thereof.

[00309] The terms “determining,” “measuring,” “evaluating,” “assessing,” “assaying,” and “analyzing” are often used interchangeably herein to refer to forms of measurement. The terms include determining if an element is present or not (for example, detection). These terms can include quantitative, qualitative or quantitative and qualitative determinations. Assessing can be relative or absolute. “Detecting the presence of” can include determining the amount of something present in addition to determining whether it is present or absent depending on the context.

[00310] The terms “subject,” and “patient” may be used interchangeably herein. A “subject” can be a biological entity containing expressed genetic materials. The biological entity can be a plant, animal, or microorganism, including, for example, bacteria, viruses, fungi, and protozoa. The subject can be a mammal. The mammal can be a human. The subject may be diagnosed or suspected of being at high risk

for a disease. In some cases, the subject is not necessarily diagnosed or suspected of being at high risk for the disease.

[00311] As used herein, the term “about” a number refers to that number plus or minus 10% of that number. The term “about” a range refers to that range minus 10% of its lowest value and plus 10% of its greatest value.

[00312] As used herein, the terms “treatment” or “treating” are used in reference to a pharmaceutical or other intervention regimen for obtaining beneficial or desired results in the recipient. Beneficial or desired results include but are not limited to a therapeutic benefit and/or a prophylactic benefit. A therapeutic benefit may refer to eradication or amelioration of symptoms or of an underlying disorder being treated. Also, a therapeutic benefit can be achieved with the eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. A prophylactic effect includes delaying, preventing, or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. For prophylactic benefit, a subject at risk of developing a particular disease, or to a subject reporting one or more of the symptoms of a disease may undergo treatment, even though a diagnosis of this disease may not have been made.

[00313] Some embodiments refer to nucleic acid sequence information. It is contemplated that in some embodiments, thymine (T) may be interchanged with uracil (U), or vice versa. For example, some sequences in the sequence listing may recite Ts, but these may be replaced with Us in some embodiments. In some oligonucleotides with nucleic acid sequences that include uracil, the uracil may be replaced with thymine. Similarly, in some oligonucleotides with nucleic acid sequences that include thymine, the thymine may be replaced with uracil. In some embodiments, an oligonucleotide such as an siRNA comprises or consists of RNA. In some embodiments, the oligonucleotide may comprise or consist of DNA. For example, an ASO may include DNA.

[00314] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

VI. EXAMPLES

Example 1: Functional variants in FGG demonstrate protective associations for psychiatric and neurodegenerative diseases

[00315] Variants in FGG were evaluated for associations with psychiatric diseases and neurological diseases, and related traits in approximately 382,000 individuals with genotype data from the UK Biobank cohort. Variants evaluated included: (1) rs148685782, a rare (AAF=0.004) FGG missense variant (Ala108Gly; A108G), which has been experimentally characterized as a FGG ↓ pQTL and (2) rs6063, a rare (AAF=0.005) FGG missense variant (Gly191Arg; G191R), which may have a deleterious impact on the FGG protein. Both variants were considered hypomorphic or loss-of-function variants that result in a

decrease in the abundance or activity of the FGG gene product. Also evaluated was an FGG gene burden test which aggregated rs148685782, rs6063 and several additional rare nonsynonymous variants in FGG. [00316] The analyses presented used a logistic or linear regression model with age, sex and the first ten principal components of genetic ancestry as covariates. The analyses resulted in identification of associations for the individual FGG variants and the FGG gene burden (Tables 1A-1C and 2A-2B).

Table 1A. FGG psychiatric disease associations

Variant	Gene	Function	AAF	Major Depressive Disorder (n=35,446)	
				P value	OR
rs148685782	FGG	Missense A108G; FGG ↓pQTL	0.004	0.004	↓0.861
rs6063	FGG	Missense G191R	0.005	0.003	↓0.848
Gene Burden	FGG	Aggregation of rare deleterious variants	0.009	6.45E-06	↓0.857

Table 1B. FGG psychiatric disease associations

Variant	SSRI Medication (n=40,721)		Intentional Self Harm (n=2,395)	
	P value	OR	P value	OR
rs148685782	0.01	↓0.906	8.14E-04	↓0.359
rs6063	0.015	↓0.917	0.201	↓0.760
Gene Burden	1.64E-04	↓0.907	0.002	↓0.575

Table 1C. FGG psychiatric disease associations

Variant	Family History of Severe Depression (n=49,923)		Post-Traumatic Stress Disorder (n=672)	
	P value	OR	P value	OR
rs148685782	0.135	↓0.920	0.072	↓0.509
rs6063	0.063	↓0.907	0.032	↓0.454
Gene Burden	0.032	↓0.922	0.009	↓0.508

Table 2A. FGG neurological disease associations

Variant	Gene	Function	AAF	Alzheimer's Disease (n=1,995)	
				P value	OR
rs148685782	FGG	Missense A108G; FGG ↓pQTL	0.004	0.031	↓0.562
rs6063	FGG	Missense G191R	0.005	0.058	↓0.635
Gene Burden	FGG	Aggregation of rare deleterious variants	0.009	0.006	↓0.604

Table 2B. FGG neurological disease associations

Variant	Early-Onset Alzheimer's Disease (n=190)		Dementia (n=4,283)		Headache (n=25,534)	
	P value	OR	P value	OR	P value	OR
rs148685782	0.275	↓0.513	0.034	↓0.739	3.03E-04	↓0.835
rs6063	0.182	↓0.446	0.068	↓0.779	0.605	↓0.980
Gene Burden	0.026	↓0.229	0.012	↓0.783	0.004	↓0.911

[00317] The data demonstrated that there were protective associations with multiple psychiatric and depression-related traits (shown in **Tables 1A-1C**). The rs148685782 (A108G) variant, the rs6063 (G191R) variant, and the FGG gene burden were all associated with protection from major depressive disorder. Additionally, evaluated FGG variants were individually and collectively associated with decreased risk of SSRI medication-use, intentional self-harm, a family history of severe depression and post-traumatic stress disorder.

[00318] Additionally, there were protective associations with multiple neurological and dementia-related traits (shown in **Table 2A-2B**). The rs148685782 (A108G) variant, the rs6063 (G191R) variant and the FGG gene burden were individually and collectively associated with decreased risk of Alzheimer's Disease, early-onset Alzheimer's Disease, all-cause dementia and headache disorders.

[00319] These results indicate that loss-of-function of FGG resulted in protection from a range of psychiatric disorders, including depressive disorders, and from a range of neurological disorders, including Alzheimer's Disease; and suggest that therapeutic inhibition of FGG may result in similar disease-protective effects.

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

[00320] Screening sets were defined based on bioinformatic analysis. Therapeutic siRNAs were designed to target human FGG, and the FGG sequence of at least one toxicology-relevant species; in this case, non-human primates (NHP) including rhesus and cynomolgus monkeys. Drivers for the design of the screening set were predicted specificity of the siRNAs against the transcriptome of the relevant species as well as cross-reactivity between species. Predicted specificity in human, rhesus monkey, cynomolgus monkey, mouse, rat, rabbit, dog, gerbil, Syrian hamster, Chinese hamster, guinea pig, and naked mole rat was determined for sense (S) and antisense (AS) strands. These were assigned a "specificity score" which considered the likelihood of unintended downregulation of any other transcript by full or partial complementarity of an siRNA strand (up to 2 mismatches within positions 2-18) as well as the number and positions of mismatches. Thus, off-target(s) transcripts for antisense and sense strands of each siRNA were identified. In addition, the number of potential off-targets was used as an additional specificity factor in the specificity score. As identified, siRNAs with high specificity and a low number of predicted off-targets provide a benefit of increased targeting specificity.

[00321] In addition to selecting siRNA sequences with high sequence specificity to FGG mRNA, siRNA sequences within the seed region were analyzed for similarity to seed regions of known miRNAs. siRNAs can function in a miRNA like manner via base-pairing with complementary sequences within the 3'-UTR of mRNA molecules. The complementarity typically encompassed the 5'-bases at positions 2-7 of the miRNA (seed region). To circumvent siRNAs to act via functional miRNA binding sites, siRNA strands containing natural miRNA seed regions can be avoided. Seed regions identified in miRNAs from human, mouse, rat, rhesus monkey, dog, rabbit and pig are referred to as "conserved". Combining the "specificity score" with miRNA seed analysis yielded a "specificity category". This was divided into

categories 1-4, with 1 having the highest specificity and 4 having the lowest specificity. Each strand of the siRNA was assigned to a specificity category.

[00322] Specificity and species cross-reactivity was assessed for human, rhesus monkey, cynomolgus monkey, mouse, rat, rabbit, dog, gerbil, Syrian hamster, Chinese hamster, guinea pig and naked mole rat FGG. The analysis was based on a canonical siRNA design using 19 bases and 17 bases (without considering positions 1 and 19) for cross-reactivity. Full match as well as single mismatch analyses were included.

[00323] Analysis of the Genome Aggregation Database (gnomAD, available at gnomad.broadinstitute.org/) to identify siRNAs targeting regions with known SNPs was also carried out to identify siRNAs that may be non-functional in individuals containing the SNP. Information regarding the positions of SNPs within the target sequence as well as minor allele frequency (MAF) in case data was obtained in this analysis.

[00324] Initial analysis of the relevant FGG mRNA sequence revealed few sequences that fulfil the specificity parameters and at the same time target FGG mRNA in all of the analyzed relevant species. Therefore, it was decided to design independent screening subsets for the therapeutic siRNAs.

[00325] The siRNAs in these subsets were selected based on the ability to recognize at least the human, cynomolgus monkey, rhesus monkey FGG sequences. Therefore, the siRNAs in these subsets may be used to target human FGG in a therapeutic setting.

[00326] The number of siRNA sequences derived from human FGG mRNA (ENST00000404648, SEQ ID NO: 3621) without consideration of specificity or species cross-reactivity was 1742 (sense and antisense strand sequences included in SEQ ID NOS: 1-3484).

[00327] Prioritizing sequences for target specificity, species cross-reactivity, miRNA seed region sequences and SNPs as described above yielded subset A. Subset A includes 319 siRNAs whose base sequences are shown in **Table 3**.

Table 3: Subset A siRNAs

siRNA Name	Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 224	224	CCGGGCACTCAGACATCAT	1966	ATGATGTCTGAGTGCCCGG
siRNA 233	233	CAGACATCATGAGTTGGTC	1975	GACCAACTCATGATGTCTG
siRNA 234	234	AGACATCATGAGTTGGTCC	1976	GGACCAACTCATGATGTCT
siRNA 235	235	GACATCATGAGTTGGTCCT	1977	AGGACCAACTCATGATGTC
siRNA 248	248	GGTCCTTGACCCCCCGGAA	1990	TTCCGGGGGTGCAAGGACC
siRNA 249	249	GTCCCTTGACCCCCCGGAAT	1991	ATTCCGGGGGTGCAAGGAC
siRNA 250	250	TCCTTGACCCCCCGGAATT	1992	AATTCCGGGGGTGCAAGGA
siRNA 251	251	CCTTGACCCCCCGGAATTT	1993	AAATTCCGGGGGTGCAAGG
siRNA 253	253	TTGCACCCCCCGGAATTTAA	1995	TTAAATTCCGGGGGTGCAA
siRNA 254	254	TGCACCCCCCGGAATTTAAT	1996	ATTAAATTCCGGGGGTGCA
siRNA 255	255	GCACCCCCCGGAATTTAATT	1997	AATTAAATTCCGGGGGTGC
siRNA 258	258	CCCCCGGAATTTAATTCTC	2000	GAGAATTAAATTCCGGGGG
siRNA 260	260	CCCGGAATTTAATTCTCTA	2002	TAGAGAATTAAATTCCGGG

siRNA 261	261	CCGGAATTTAATTCTCTAC	2003	GTAGAGAATTAAATTCCGG
siRNA 262	262	CGGAATTTAATTCTCTACT	2004	AGTAGAGAATTAAATTCCG
siRNA 269	269	TAATTCTCTACTTCTATGC	2011	GCATAGAAGTAGAGAATTA
siRNA 273	273	TCTCTACTTCTATGCTCTT	2015	AAGAGCATAGAAGTAGAGA
siRNA 274	274	CTCTACTTCTATGCTCTTT	2016	AAAGAGCATAGAAGTAGAG
siRNA 275	275	TCTACTTCTATGCTCTTTT	2017	AAAAGAGCATAGAAGTAGA
siRNA 297	297	TCTCTCTTCAACATGTGTA	2039	TACACATGTTGAAGAGAGA
siRNA 310	310	TGTGTAGCATATGTTGCTA	2052	TAGCAACATATGCTACACA
siRNA 311	311	GTGTAGCATATGTTGCTAC	2053	GTAGCAACATATGCTACAC
siRNA 319	319	TATGTTGCTACCAGAGACA	2061	TGTCTCTGGTAGCAACATA
siRNA 322	322	GTTGCTACCAGAGACAACT	2064	AGTTGTCTCTGGTAGCAAC
siRNA 323	323	TTGCTACCAGAGACAACTG	2065	CAGTTGTCTCTGGTAGCAA
siRNA 324	324	TGCTACCAGAGACAACTGC	2066	GCAGTTGTCTCTGGTAGCA
siRNA 329	329	CCAGAGACAACTGCTGCAT	2071	ATGCAGCAGTTGTCTCTGG
siRNA 335	335	ACAACTGCTGCATCTTAGA	2077	TCTAAGATGCAGCAGTTGT
siRNA 342	342	CTGCATCTTAGATGAAAGA	2084	TCTTTCATCTAAGATGCAG
siRNA 343	343	TGCATCTTAGATGAAAGAT	2085	ATCTTTCATCTAAGATGCA
siRNA 344	344	GCATCTTAGATGAAAGATT	2086	AATCTTTCATCTAAGATGC
siRNA 347	347	TCTTAGATGAAAGATTTCGG	2089	CCGAATCTTTCATCTAAGA
siRNA 348	348	CTTAGATGAAAGATTTCGGT	2090	ACCGAATCTTTCATCTAAG
siRNA 349	349	TTAGATGAAAGATTTCGGTA	2091	TACCGAATCTTTCATCTAA
siRNA 350	350	TAGATGAAAGATTTCGGTAG	2092	CTACCGAATCTTTCATCTA
siRNA 351	351	AGATGAAAGATTTCGGTAGT	2093	ACTACCGAATCTTTCATCT
siRNA 352	352	GATGAAAGATTTCGGTAGTT	2094	AACTACCGAATCTTTCATC
siRNA 354	354	TGAAAGATTTCGGTAGTTAT	2096	ATAACTACCGAATCTTTC
siRNA 355	355	GAAAGATTTCGGTAGTTATT	2097	AATAACTACCGAATCTTTC
siRNA 359	359	GATTTCGGTAGTTATTGTCC	2101	GGACAATAACTACCGAATC
siRNA 361	361	TTCGGTAGTTATTGTCCAA	2103	TTGGACAATAACTACCGAA
siRNA 362	362	TCGGTAGTTATTGTCCAAC	2104	GTTGGACAATAACTACCGA
siRNA 363	363	CGGTAGTTATTGTCCAACCT	2105	AGTTGGACAATAACTACCG
siRNA 364	364	GGTAGTTATTGTCCAACCTA	2106	TAGTTGGACAATAACTACC
siRNA 365	365	GTAGTTATTGTCCAACCTAC	2107	GTAGTTGGACAATAACTAC
siRNA 366	366	TAGTTATTGTCCAACCTACC	2108	GGTAGTTGGACAATAACTA
siRNA 367	367	AGTTATTGTCCAACCTACCT	2109	AGGTAGTTGGACAATAACT
siRNA 369	369	TTATTGTCCAACCTACCTGT	2111	ACAGGTAGTTGGACAATAA
siRNA 372	372	TTGTCCAACCTACCTGTGGC	2114	GCCACAGGTAGTTGGACAA
siRNA 373	373	TGTCCAACCTACCTGTGGCA	2115	TGCCACAGGTAGTTGGACA
siRNA 384	384	CTGTGGCATTGCAGATTTC	2126	GAAATCTGCAATGCCACAG
siRNA 386	386	GTGGCATTGCAGATTTCCT	2128	AGGAAATCTGCAATGCCAC
siRNA 392	392	TTGCAGATTTCCTGTCTAC	2134	GTAGACAGGAAATCTGCAA
siRNA 397	397	GATTTCTGTCTACTTATC	2139	GATAAGTAGACAGGAAATC
siRNA 398	398	ATTTCTGTCTACTTATCA	2140	TGATAAGTAGACAGGAAAT
siRNA 399	399	TTTCCTGTCTACTTATCAA	2141	TTGATAAGTAGACAGGAAA
siRNA 406	406	TCTACTTATCAAACCAAAG	2148	CTTTGGTTTGATAAGTAGA
siRNA 411	411	TTATCAAACCAAAGTAGAC	2153	GTCTACTTTGGTTTGATAA
siRNA 412	412	TATCAAACCAAAGTAGACA	2154	TGTCTACTTTGGTTTGATA
siRNA 423	423	AGTAGACAAGGATCTACAG	2165	CTGTAGATCCTTGTCTACT
siRNA 426	426	AGACAAGGATCTACAGTCT	2168	AGACTGTAGATCCTTGTCT

siRNA 432	432	GGATCTACAGTCTTTGGAA	2174	TTCCAAAGACTGTAGATCC
siRNA 434	434	ATCTACAGTCTTTGGAAGA	2176	TCTTCCAAAGACTGTAGAT
siRNA 437	437	TACAGTCTTTGGAAGACAT	2179	ATGTCTTCCAAAGACTGTA
siRNA 447	447	GGAAGACATCTTACATCAA	2189	TTGATGTAAGATGTCTTCC
siRNA 449	449	AAGACATCTTACATCAAGT	2191	ACTTGATGTAAGATGTCTT
siRNA 450	450	AGACATCTTACATCAAGTT	2192	AACTTGATGTAAGATGTCT
siRNA 493	493	CAGCTGATAAAAAGCAATCC	2235	GGATTGCTTTTATCAGCTG
siRNA 494	494	AGCTGATAAAAAGCAATCCA	2236	TGGATTGCTTTTATCAGCT
siRNA 497	497	TGATAAAAAGCAATCCAACT	2239	AGTTGGATTGCTTTTATCA
siRNA 504	504	AGCAATCCAACTCACTTAT	2246	ATAAGTGAGTTGGATTGCT
siRNA 505	505	GCAATCCAACTCACTTATA	2247	TATAAGTGAGTTGGATTGC
siRNA 507	507	AATCCAACTCACTTATAAT	2249	ATTATAAGTGAGTTGGATT
siRNA 508	508	ATCCAACTCACTTATAATC	2250	GATTATAAGTGAGTTGGAT
siRNA 509	509	TCCAACTCACTTATAATCC	2251	GGATTATAAGTGAGTTGGA
siRNA 510	510	CCAACTCACTTATAATCCT	2252	AGGATTATAAGTGAGTTGG
siRNA 511	511	CAACTCACTTATAATCCTG	2253	CAGGATTATAAGTGAGTTG
siRNA 514	514	CTCACTTATAATCCTGATG	2256	CATCAGGATTATAAGTGAG
siRNA 515	515	TCACTTATAATCCTGATGA	2257	TCATCAGGATTATAAGTGA
siRNA 522	522	TAATCCTGATGAATCATCA	2264	TGATGATTCATCAGGATTA
siRNA 523	523	AATCCTGATGAATCATCAA	2265	TTGATGATTCATCAGGATT
siRNA 528	528	TGATGAATCATCAAAACCA	2270	TGGTTTTGATGATTCATCA
siRNA 539	539	CAAAACCAAATATGATAGA	2281	TCTATCATATTTGGTTTTG
siRNA 541	541	AAACCAAATATGATAGACG	2283	CGTCTATCATATTTGGTTT
siRNA 544	544	CCAAATATGATAGACGCTG	2286	CAGCGTCTATCATATTTGG
siRNA 546	546	AAATATGATAGACGCTGCT	2288	AGCAGCGTCTATCATATTT
siRNA 548	548	ATATGATAGACGCTGCTAC	2290	GTAGCAGCGTCTATCATAT
siRNA 554	554	TAGACGCTGCTACTTTGAA	2296	TTCAAAGTAGCAGCGTCTA
siRNA 556	556	GACGCTGCTACTTTGAAGT	2298	ACTTCAAAGTAGCAGCGTC
siRNA 573	573	GTCCAGGAAAATGTTAGAA	2315	TTCTAACATTTTCTGGAC
siRNA 599	599	TGAAATATGAAGCATCGAT	2341	ATCGATGCTTCATATTTCA
siRNA 600	600	GAAATATGAAGCATCGATT	2342	AATCGATGCTTCATATTTT
siRNA 601	601	AAATATGAAGCATCGATTT	2343	AAATCGATGCTTCATATTT
siRNA 604	604	TATGAAGCATCGATTTTAA	2346	TTAAAAATCGATGCTTCATA
siRNA 606	606	TGAAGCATCGATTTTAACA	2348	TGTTAAAAATCGATGCTTCA
siRNA 607	607	GAAGCATCGATTTTAACAC	2349	GTGTTAAAAATCGATGCTTC
siRNA 608	608	AAGCATCGATTTTAACACA	2350	TGTGTTAAAAATCGATGCTT
siRNA 609	609	AGCATCGATTTTAACACAT	2351	ATGTGTTAAAAATCGATGCT
siRNA 619	619	TTAACACATGACTCAAGTA	2361	TACTTGAGTCATGTGTTAA
siRNA 624	624	ACATGACTCAAGTATTCGA	2366	TCGAATACTTGAGTCATGT
siRNA 625	625	CATGACTCAAGTATTCGAT	2367	ATCGAATACTTGAGTCATG
siRNA 633	633	AAGTATTCGATATTTGCAG	2375	CTGCAAAATATCGAATACTT
siRNA 634	634	AGTATTCGATATTTGCAGG	2376	CCTGCAAAATATCGAATACT
siRNA 661	661	AATTCAAATAATCAAAAAGA	2403	TCTTTTGATTATTTGAATT
siRNA 689	689	TGAAAGAGAAGGTAGCCCA	2431	TGGGCTACCTTCTCTTTCA
siRNA 691	691	AAAGAGAAGGTAGCCCAGC	2433	GCTGGGCTACCTTCTCTTT
siRNA 709	709	CTTGAAGCACAGTGCCAGG	2451	CCTGGCACTGTGCTTCAAG
siRNA 716	716	CACAGTGCCAGGAACCTTG	2458	CAAGGTTCTTGGCACTGTG
siRNA 720	720	GTGCCAGGAACCTTGCAAA	2462	TTTGCAAGGTTCTTGGCAC

siRNA 724	724	CAGGAACCTTGCAAAGACA	2466	TGTCTTTGCAAGGTTCTG
siRNA 728	728	AACCTTGCAAAGACACGGT	2470	ACCGTGTCTTTGCAAGGTT
siRNA 729	729	ACCTTGCAAAGACACGGTG	2471	CACCGTGTCTTTGCAAGGT
siRNA 730	730	CCTTGCAAAGACACGGTGC	2472	GCACCGTGTCTTTGCAAGG
siRNA 731	731	CTTGCAAAGACACGGTGCA	2473	TGCACCGTGTCTTTGCAAG
siRNA 732	732	TTGCAAAGACACGGTGCAA	2474	TTGCACCGTGTCTTTGCAA
siRNA 733	733	TGCAAAGACACGGTGCAAA	2475	TTTGACCGTGTCTTTGCA
siRNA 734	734	GCAAAGACACGGTGCAAAT	2476	ATTTGCACCGTGTCTTTGC
siRNA 736	736	AAAGACACGGTGCAAATCC	2478	GGATTTGCACCGTGTCTTT
siRNA 748	748	CAAATCCATGATATCACTG	2490	CAGTGATATCATGGATTTG
siRNA 749	749	AAATCCATGATATCACTGG	2491	CCAGTGATATCATGGATTT
siRNA 751	751	ATCCATGATATCACTGGGA	2493	TCCCAGTGATATCATGGAT
siRNA 752	752	TCCATGATATCACTGGGAA	2494	TTCCCAGTGATATCATGGA
siRNA 753	753	CCATGATATCACTGGGAAA	2495	TTTCCCAGTGATATCATGG
siRNA 770	770	AAGATTGTCAAGACATTGC	2512	GCAATGTCTTGACAATCTT
siRNA 778	778	CAAGACATTGCCAATAAGG	2520	CCTTATTGGCAATGTCTTG
siRNA 780	780	AGACATTGCCAATAAGGGA	2522	TCCCTTATTGGCAATGTCT
siRNA 783	783	CATTGCCAATAAGGGAGCT	2525	AGCTCCCTTATTGGCAATG
siRNA 784	784	ATTGCCAATAAGGGAGCTA	2526	TAGCTCCCTTATTGGCAAT
siRNA 785	785	TTGCCAATAAGGGAGCTAA	2527	TTAGCTCCCTTATTGGCAA
siRNA 786	786	TGCCAATAAGGGAGCTAAA	2528	TTTAGCTCCCTTATTGGCA
siRNA 791	791	ATAAGGGAGCTAAACAGAG	2533	CTCTGTTTAGCTCCCTTAT
siRNA 794	794	AGGGAGCTAAACAGAGCGG	2536	CCGCTCTGTTTAGCTCCCT
siRNA 795	795	GGGAGCTAAACAGAGCGGG	2537	CCCGCTCTGTTTAGCTCCC
siRNA 796	796	GGAGCTAAACAGAGCGGGC	2538	GCCCGCTCTGTTTAGCTCC
siRNA 797	797	GAGCTAAACAGAGCGGGCT	2539	AGCCCGCTCTGTTTAGCTC
siRNA 800	800	CTAAACAGAGCGGGCTTTA	2542	TAAAGCCCGCTCTGTTTAG
siRNA 802	802	AAACAGAGCGGGCTTTACT	2544	AGTAAAGCCCGCTCTGTTT
siRNA 805	805	CAGAGCGGGCTTTACTTTA	2547	TAAAGTAAAGCCCGCTCTG
siRNA 806	806	AGAGCGGGCTTTACTTTAT	2548	ATAAAGTAAAGCCCGCTCT
siRNA 812	812	GGCTTTACTTTATTAAACC	2554	GGTTTAATAAAGTAAAGCC
siRNA 821	821	TTATTAAACCTCTGAAAGC	2563	GCTTTCAGAGGTTTAATAA
siRNA 822	822	TATTAAACCTCTGAAAGCT	2564	AGCTTTCAGAGGTTTAATA
siRNA 825	825	TAAACCTCTGAAAGCTAAC	2567	GTTAGCTTTCAGAGGTTTA
siRNA 826	826	AAACCTCTGAAAGCTAACC	2568	GGTAGCTTTCAGAGGTTT
siRNA 827	827	AACCTCTGAAAGCTAACCA	2569	TGGTAGCTTTCAGAGGTT
siRNA 828	828	ACCTCTGAAAGCTAACCAG	2570	CTGGTAGCTTTCAGAGGT
siRNA 833	833	TGAAAGCTAACCAGCAATT	2575	AATTGCTGGTTAGCTTTCA
siRNA 841	841	AACCAGCAATTCTTAGTCT	2583	AGACTAAGAATTGCTGGTT
siRNA 844	844	CAGCAATTCTTAGTCTACT	2586	AGTAGACTAAGAATTGCTG
siRNA 850	850	TTCTTAGTCTACTGTGAAA	2592	TTTCACAGTAGACTAAGAA
siRNA 860	860	ACTGTGAAATCGATGGGTC	2602	GACCCATCGATTTACAGT
siRNA 861	861	CTGTGAAATCGATGGGTCT	2603	AGACCCATCGATTTACAG
siRNA 865	865	GAAATCGATGGGTCTGGAA	2607	TTCCAGACCCATCGATTT
siRNA 866	866	AAATCGATGGGTCTGGAAA	2608	TTTCCAGACCCATCGATTT
siRNA 877	877	TCTGGAAATGGATGGACTG	2619	CAGTCCATCCATTCCAGA
siRNA 893	893	CTGTGTTTCAGAAGAGACT	2635	AGTCTCTTCTGAAACACAG
siRNA 894	894	TGTGTTTCAGAAGAGACTT	2636	AAGTCTCTTCTGAAACACA

siRNA 904	904	AAGAGACTTGATGGCAGTG	2646	CACTGCCATCAAGTCTCTT
siRNA 916	916	GGCAGTGTAGATTTCAAGA	2658	TCTTGAAATCTACACTGCC
siRNA 929	929	TCAAGAAAACTGGATTCA	2671	TGAATCCAGTTTTTCTTGA
siRNA 932	932	AGAAAACTGGATTCAATA	2674	TATTGAATCCAGTTTTTCT
siRNA 955	955	GAAGGATTTGGACATCTGT	2697	ACAGATGTCCAAATCCTTC
siRNA 956	956	AAGGATTTGGACATCTGTC	2698	GACAGATGTCCAAATCCTT
siRNA 963	963	TGGACATCTGTCTCCTACT	2705	AGTAGGAGACAGATGTCCA
siRNA 964	964	GGACATCTGTCTCCTACTG	2706	CAGTAGGAGACAGATGTCC
siRNA 966	966	ACATCTGTCTCCTACTGGC	2708	GCCAGTAGGAGACAGATGT
siRNA 969	969	TCTGTCTCCTACTGGACA	2711	TGTGCCAGTAGGAGACAGA
siRNA 972	972	GTCTCCTACTGGACAACA	2714	TGTTGTGCCAGTAGGAGAC
siRNA 973	973	TCTCCTACTGGACAACAG	2715	CTGTTGTGCCAGTAGGAGA
siRNA 983	983	GCACAACAGAATTTTGGCT	2725	AGCCAAAATTCTGTTGTGC
siRNA 1003	1003	GGAAATGAGAAGATTTCATT	2745	AATGAATCTTCTCATTTCC
siRNA 1011	1011	GAAGATTCATTTGATAAGC	2753	GCTTATCAAATGAATCTTC
siRNA 1013	1013	AGATTCATTTGATAAGCAC	2755	GTGCTTATCAAATGAATCT
siRNA 1022	1022	TGATAAGCACACAGTCTGC	2764	GCAGACTGTGTGCTTATCA
siRNA 1024	1024	ATAAGCACACAGTCTGCCA	2766	TGGCAGACTGTGTGCTTAT
siRNA 1025	1025	TAAGCACACAGTCTGCCAT	2767	ATGGCAGACTGTGTGCTTA
siRNA 1027	1027	AGCACACAGTCTGCCATCC	2769	GGATGGCAGACTGTGTGCT
siRNA 1041	1041	CATCCCATATGCATTAAGA	2783	TCTTAATGCATATGGGATG
siRNA 1046	1046	CATATGCATTAAGAGTGGA	2788	TCCACTCTTAATGCATATG
siRNA 1047	1047	ATATGCATTAAGAGTGGA	2789	TTCCACTCTTAATGCATAT
siRNA 1052	1052	CATTAAGAGTGGAAGTGG	2794	TCCAGTTCCTCTTAATG
siRNA 1060	1060	GTGGAAGTGGAAAGTGG	2802	TCCAGTCTCCAGTTCAC
siRNA 1071	1071	AGACTGGAATGGCAGAACC	2813	GGTCTGCCATTCCAGTCT
siRNA 1079	1079	ATGGCAGAACCAGTACTGC	2821	GCAGTACTGGTTCTGCCAT
siRNA 1085	1085	GAACCACTACTGCAGACTA	2827	TAGTCTGCAGTACTGGTTC
siRNA 1088	1088	CCAGTACTGCAGACTATGC	2830	GCATAGTCTGCAGTACTGG
siRNA 1089	1089	CAGTACTGCAGACTATGCC	2831	GGCATAGTCTGCAGTACTG
siRNA 1091	1091	GTAAGTGCAGACTATGCCAT	2833	ATGGCATAGTCTGCAGTAC
siRNA 1095	1095	TGCAGACTATGCCATGTTT	2837	GAACATGGCATAGTCTGCA
siRNA 1110	1110	GTTCAAGGTGGGACCTGAA	2852	TTCAGGTCCCACCTTGAAC
siRNA 1111	1111	TTCAAGGTGGGACCTGAAG	2853	CTTCAGGTCCCACCTTGAA
siRNA 1120	1120	GGACCTGAAGCTGACAAGT	2862	ACTTGTGAGCTTCAGGTCC
siRNA 1123	1123	CCTGAAGCTGACAAGTACC	2865	GGTACTTGTGAGCTTCAGG
siRNA 1126	1126	GAAGCTGACAAGTACCGCC	2868	GGCGGTACTTGTGAGCTTC
siRNA 1127	1127	AAGCTGACAAGTACCGCCT	2869	AGGCGGTACTTGTGAGCTT
siRNA 1128	1128	AGCTGACAAGTACCGCCTA	2870	TAGGCGGTACTTGTGAGCT
siRNA 1129	1129	GCTGACAAGTACCGCCTAA	2871	TTAGGCGGTACTTGTGAGC
siRNA 1130	1130	CTGACAAGTACCGCCTAAC	2872	GTTAGGCGGTACTTGTGAG
siRNA 1131	1131	TGACAAGTACCGCCTAACA	2873	TGTTAGGCGGTACTTGTCA
siRNA 1132	1132	GACAAGTACCGCCTAACAT	2874	ATGTTAGGCGGTACTTGTTC
siRNA 1133	1133	ACAAGTACCGCCTAACATA	2875	TATGTTAGGCGGTACTTGT
siRNA 1134	1134	CAAGTACCGCCTAACATAT	2876	ATATGTTAGGCGGTACTTGT
siRNA 1135	1135	AAGTACCGCCTAACATATG	2877	CATATGTTAGGCGGTACTT
siRNA 1136	1136	AGTACCGCCTAACATATGC	2878	GCATATGTTAGGCGGTACT
siRNA 1137	1137	GTACCGCCTAACATATGCC	2879	GGCATATGTTAGGCGGTACT

siRNA 1138	1138	TACCGCCTAACATATGCCT	2880	AGGCATATGTTAGGCGGTA
siRNA 1139	1139	ACCGCCTAACATATGCCTA	2881	TAGGCATATGTTAGGCGGT
siRNA 1140	1140	CCGCCTAACATATGCCTAC	2882	GTAGGCATATGTTAGGCGG
siRNA 1141	1141	CGCCTAACATATGCCTACT	2883	AGTAGGCATATGTTAGGCG
siRNA 1143	1143	CCTAACATATGCCTACTTC	2885	GAAGTAGGCATATGTTAGG
siRNA 1146	1146	AACATATGCCTACTTCGCT	2888	AGCGAAGTAGGCATATGTT
siRNA 1147	1147	ACATATGCCTACTTCGCTG	2889	CAGCGAAGTAGGCATATGT
siRNA 1148	1148	CATATGCCTACTTCGCTGG	2890	CCAGCGAAGTAGGCATATG
siRNA 1149	1149	ATATGCCTACTTCGCTGGT	2891	ACCAGCGAAGTAGGCATAT
siRNA 1151	1151	ATGCCTACTTCGCTGGTGG	2893	CCACCAGCGAAGTAGGCAT
siRNA 1174	1174	GCTGGAGATGCCTTTGATG	2916	CATCAAAGGCATCTCCAGC
siRNA 1178	1178	GAGATGCCTTTGATGGCTT	2920	AAGCCATCAAAGGCATCTC
siRNA 1182	1182	TGCCTTTGATGGCTTTGAT	2924	ATCAAAGCCATCAAAGGCA
siRNA 1197	1197	TGATTTTGGCGATGATCCT	2939	AGGATCATCGCCAAAATCA
siRNA 1198	1198	GATTTTGGCGATGATCCTA	2940	TAGGATCATCGCCAAAATC
siRNA 1203	1203	TGGCGATGATCCTAGTGAC	2945	GTCCTAGGATCATCGCCA
siRNA 1205	1205	GCGATGATCCTAGTGACAA	2947	TTGTCACTAGGATCATCGC
siRNA 1206	1206	CGATGATCCTAGTGACAAG	2948	CTTGTCCTAGGATCATCG
siRNA 1215	1215	TAGTGACAAGTTTTCACA	2957	TGTGAAAAACTTGTCTACTA
siRNA 1227	1227	TTTCACATCCCATAATGGC	2969	GCCATTATGGGATGTGAAA
siRNA 1236	1236	CCATAATGGCATGCAGTTC	2978	GAAGTGCATGCCATTATGG
siRNA 1242	1242	TGGCATGCAGTTCAGTACC	2984	GGTACTGAACTGCATGCCA
siRNA 1243	1243	GGCATGCAGTTCAGTACCT	2985	AGGTACTGAACTGCATGCC
siRNA 1248	1248	GCAGTTCAGTACCTGGGAC	2990	GTCCCAGGTACTGAACTGC
siRNA 1249	1249	CAGTTCAGTACCTGGGACA	2991	TGTCCCAGGTACTGAACTG
siRNA 1264	1264	GACAATGACAATGATAAGT	3006	ACTTATCATTGTCTATTGTC
siRNA 1265	1265	ACAATGACAATGATAAGTT	3007	AACTTATCATTGTCTATTGT
siRNA 1278	1278	TAAGTTTGAAGGCAACTGT	3020	ACAGTTGCCTTCAAACCTTA
siRNA 1286	1286	AAGGCAACTGTGCTGAACA	3028	TGTTTCAGCACAGTTGCCTT
siRNA 1287	1287	AGGCAACTGTGCTGAACAG	3029	CTGTTTCAGCACAGTTGCCT
siRNA 1298	1298	CTGAACAGGATGGATCTGG	3040	CCAGATCCATCCTGTTTCAG
siRNA 1304	1304	AGGATGGATCTGGTTGGTG	3046	CACCAACCAGATCCATCCT
siRNA 1311	1311	ATCTGGTTGGTGGATGAAC	3053	GTTTCATCCACCAACCAGAT
siRNA 1315	1315	GGTTGGTGGATGAACAAGT	3057	ACTTGTTCATCCACCAACC
siRNA 1319	1319	GGTGGATGAACAAGTGTC	3061	TGACACTTGTTCATCCACC
siRNA 1320	1320	GTGGATGAACAAGTGTCAC	3062	GTGACACTTGTTCATCCAC
siRNA 1323	1323	GATGAACAAGTGTCACGCT	3065	AGCGTGACACTTGTTCATC
siRNA 1324	1324	ATGAACAAGTGTCACGCTG	3066	CAGCGTGACACTTGTTCAT
siRNA 1325	1325	TGAACAAGTGTCACGCTGG	3067	CCAGCGTGACACTTGTTC
siRNA 1326	1326	GAACAAGTGTCACGCTGGC	3068	GCCAGCGTGACACTTGTTC
siRNA 1339	1339	GCTGGCCATCTCAATGGAG	3081	CTCCATTGAGATGGCCAGC
siRNA 1342	1342	GGCCATCTCAATGGAGTTT	3084	AAACTCCATTGAGATGGCC
siRNA 1344	1344	CCATCTCAATGGAGTTTAT	3086	ATAAACTCCATTGAGATGG
siRNA 1348	1348	CTCAATGGAGTTTATTACC	3090	GGTAATAAACTCCATTGAG
siRNA 1349	1349	TCAATGGAGTTTATTACCA	3091	TGGTAATAAACTCCATTGA
siRNA 1354	1354	GGAGTTTATTACCAAGGTG	3096	CACCTTGGTAATAAACTCC
siRNA 1356	1356	AGTTTATTACCAAGGTGGC	3098	GCCACCTTGGTAATAAACT
siRNA 1359	1359	TTATTACCAAGGTGGCACT	3101	AGTGCCACCTTGGTAATAA

siRNA 1362	1362	TTACCAAGGTGGCACTTAC	3104	GTAAGTGCCACCTTGGTAA
siRNA 1365	1365	CCAAGGTGGCACTTACTCA	3107	TGAGTAAGTGCCACCTTGG
siRNA 1368	1368	AGGTGGCACTTACTCAAAA	3110	TTTTGAGTAAGTGCCACCT
siRNA 1374	1374	CACTTACTCAAAAGCATCT	3116	AGATGCTTTTGAGTAAGTG
siRNA 1383	1383	AAAAGCATCTACTCCTAAT	3125	ATTAGGAGTAGATGCTTTT
siRNA 1384	1384	AAAGCATCTACTCCTAATG	3126	CATTAGGAGTAGATGCTTT
siRNA 1385	1385	AAGCATCTACTCCTAATGG	3127	CCATTAGGAGTAGATGCTT
siRNA 1386	1386	AGCATCTACTCCTAATGGT	3128	ACCATTAGGAGTAGATGCT
siRNA 1387	1387	GCATCTACTCCTAATGGTT	3129	AACCATTAGGAGTAGATGC
siRNA 1389	1389	ATCTACTCCTAATGGTTAT	3131	ATAACCATTAGGAGTAGAT
siRNA 1390	1390	TCTACTCCTAATGGTTATG	3132	CATAACCATTAGGAGTAGA
siRNA 1391	1391	CTACTCCTAATGGTTATGA	3133	TCATAACCATTAGGAGTAG
siRNA 1394	1394	CTCCTAATGGTTATGATAA	3136	TTATCATAACCATTAGGAG
siRNA 1395	1395	TCCTAATGGTTATGATAAT	3137	ATTATCATAACCATTAGGA
siRNA 1396	1396	CCTAATGGTTATGATAATG	3138	CATTATCATAACCATTAGG
siRNA 1401	1401	TGGTTATGATAATGGCATT	3143	AATGCCATTATCATAACCA
siRNA 1404	1404	TTATGATAATGGCATTATT	3146	AATAATGCCATTATCATAA
siRNA 1409	1409	ATAATGGCATTATTTGGGC	3151	GCCCCAAATAATGCCATTAT
siRNA 1410	1410	TAATGGCATTATTTGGGCC	3152	GGCCCCAAATAATGCCATTA
siRNA 1417	1417	ATTATTTGGGCCACTTGGGA	3159	TCCAAGTGGCCCCAAATAAT
siRNA 1418	1418	TTATTTGGGCCACTTGGAA	3160	TTCCAAGTGGCCCCAAATAA
siRNA 1419	1419	TATTTGGGCCACTTGGAAA	3161	TTTCCAAGTGGCCCCAAATA
siRNA 1420	1420	ATTTGGGCCACTTGGAAAA	3162	TTTTCCAAGTGGCCCCAAAT
siRNA 1426	1426	GCCACTTGGAAAACCCGGT	3168	ACCGGGTTTCCAAGTGGC
siRNA 1427	1427	CCACTTGGAAAACCCGGTG	3169	CACCGGGTTTCCAAGTGG
siRNA 1428	1428	CACCTTGGAAAACCCGGTGG	3170	CCACCGGGTTTCCAAGTG
siRNA 1431	1431	TTGGAAAACCCGGTGGTAT	3173	ATACCACCGGGTTTCCAA
siRNA 1432	1432	TGGAAAACCCGGTGGTATT	3174	AATACCACCGGGTTTCCA
siRNA 1434	1434	GAAAACCCGGTGGTATTCC	3176	GGAATACCACCGGGTTTTC
siRNA 1435	1435	AAAACCCGGTGGTATTCCA	3177	TGGAATACCACCGGGTTTT
siRNA 1440	1440	CCGGTGGTATTCCATGAAG	3182	CTTCATGGAATACCACCGG
siRNA 1461	1461	AACCACTATGAAGATAATC	3203	GATTATCTTCATAGTGGTT
siRNA 1462	1462	ACCACTATGAAGATAATCC	3204	GGATTATCTTCATAGTGGT
siRNA 1466	1466	CTATGAAGATAATCCCATT	3208	AATGGGATTATCTTCATAG
siRNA 1467	1467	TATGAAGATAATCCCATTC	3209	GAATGGGATTATCTTCATA
siRNA 1477	1477	ATCCCATTCAACAGACTCA	3219	TGAGTCTGTTGAATGGGAT
siRNA 1478	1478	TCCCATTCAACAGACTCAC	3220	GTGAGTCTGTTGAATGGGA
siRNA 1482	1482	ATTCAACAGACTCACAATT	3224	AATTGTGAGTCTGTTGAAT
siRNA 1485	1485	CAACAGACTCACAATTGGA	3227	TCCAATTGTGAGTCTGTTG
siRNA 1487	1487	ACAGACTCACAATTGGAGA	3229	TCTCCAATTGTGAGTCTGT
siRNA 1488	1488	CAGACTCACAATTGGAGAA	3230	TTCTCCAATTGTGAGTCTG
siRNA 1519	1519	CACCTGGGGGGAGCCAAAC	3261	GTTTGGCTCCCCCAGGTG
siRNA 1533	1533	CAAACAGGCTGGAGACGTT	3275	AACGTCTCCAGCCTGTTTG
siRNA 1540	1540	GCTGGAGACGTTTAAAGA	3282	TCTTTTAAACGTCTCCAGC
siRNA 1583	1583	TTAAAGGACTTTATCTGAA	3325	TTCAGATAAAGTCCTTTAA
siRNA 1588	1588	GGACTTTATCTGAACAGAG	3330	CTCTGTTTCAAGATAAAGTCC
siRNA 1592	1592	TTTATCTGAACAGAGAGAT	3334	ATCTCTCTGTTTCAAGATAA
siRNA 1597	1597	CTGAACAGAGAGATATAAT	3339	ATTATATCTCTCTGTTTCAAG

siRNA 1615	1615	TATTTTTCCTATTGGACAA	3357	TTGTCCAATAGGAAAAATA
siRNA 1617	1617	TTTTTCCTATTGGACAATG	3359	CATTGTCCAATAGGAAAAA
siRNA 1622	1622	CCTATTGGACAATGGACTT	3364	AAGTCCATTGTCCAATAGG
siRNA 1623	1623	CTATTGGACAATGGACTTG	3365	CAAGTCCATTGTCCAATAG
siRNA 1626	1626	TTGGACAATGGACTTGCAA	3368	TTGCAAGTCCATTGTCCAA
siRNA 1627	1627	TGGACAATGGACTTGCAAA	3369	TTTGCAAGTCCATTGTCCA
siRNA 1647	1647	CTTCACTTCATTTTAAGAG	3389	CTCTTAAAATGAAGTGAAG
siRNA 1648	1648	TTCACTTCATTTTAAGAGC	3390	GCTCTTAAAATGAAGTGAA
siRNA 1649	1649	TCACTTCATTTTAAGAGCA	3391	TGCTCTTAAAATGAAGTGA
siRNA 1664	1664	AGCAAAAGACCCCATGTTG	3406	CAACATGGGGTCTTTTGCT
siRNA 1672	1672	ACCCCATGTTGAAAACCTCC	3414	GGAGTTTCAACATGGGGT
siRNA 1678	1678	TGTTGAAAACCTCCATAACA	3420	TGTTATGGAGTTTCAACA
siRNA 1679	1679	GTTGAAAACCTCCATAACAG	3421	CTGTTATGGAGTTTCAAC
siRNA 1680	1680	TTGAAAACCTCCATAACAGT	3422	ACTGTTATGGAGTTTCAA
siRNA 1691	1691	ATAACAGTTTATGCTGAT	3433	ATCAGCATAAACTGTTAT
siRNA 1696	1696	AGTTTTATGCTGATGATAA	3438	TTATCATCAGCATAAACT
siRNA 1700	1700	TTATGCTGATGATAATTTA	3442	TAAATTATCATCAGCATAA
siRNA 1710	1710	GATAATTTATCTACATGCA	3452	TGCATGTAGATAAATTATC

[00328] The siRNAs in subset A were selected to have the following characteristics:

- Cross-reactivity: With 19mer in human FGG mRNA, with 17mer/19mer in NHP FGG
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species
- Off-target frequency: ≤ 30 human off-targets matched with 2 mismatches in antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF $\geq 1\%$ (pos. 2-18)

[00329] The siRNA sequences in subset A were selected for more stringent specificity to yield subset

B. Subset B includes 318 siRNAs whose base sequences are shown in Table 4.

Table 4: Subset B siRNAs

siRNA Name	Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 224	224	CCGGGCACTCAGACATCAT	1966	ATGATGTCTGAGTGCCCGG
siRNA 233	233	CAGACATCATGAGTTGGTC	1975	GACCAACTCATGATGTCTG
siRNA 234	234	AGACATCATGAGTTGGTCC	1976	GGACCAACTCATGATGTCT
siRNA 235	235	GACATCATGAGTTGGTCTT	1977	AGGACCAACTCATGATGTC
siRNA 248	248	GGTCCTTGCACCCCGGAA	1990	TTCCGGGGGTGCAAGGACC
siRNA 249	249	GTCCCTTGCACCCCGGAAT	1991	ATTCCGGGGGTGCAAGGAC
siRNA 250	250	TCCCTTGCACCCCGGAATT	1992	AATTCCGGGGGTGCAAGGA
siRNA 251	251	CCTTGCACCCCGGAATTT	1993	AAATTCCGGGGGTGCAAGG
siRNA 253	253	TTGCACCCCGGAATTTAA	1995	TTAAATTCCGGGGGTGCAA
siRNA 254	254	TGCACCCCGGAATTTAAT	1996	ATTAAATTCCGGGGGTGCA
siRNA 255	255	GCACCCCGGAATTTAATT	1997	AATTAAATTCCGGGGGTGC
siRNA 258	258	CCCCCGGAATTTAATTCTC	2000	GAGAATTAAATTCCGGGGG
siRNA 260	260	CCCGGAATTTAATTCTCTA	2002	TAGAGAATTAAATTCCGGG
siRNA 261	261	CCGGAATTTAATTCTCTAC	2003	GTAGAGAATTAAATTCCGG
siRNA 262	262	CGGAATTTAATTCTCTACT	2004	AGTAGAGAATTAAATTCCG
siRNA 269	269	TAATTCTCTACTTCTATGC	2011	GCATAGAAGTAGAGAATTA

siRNA 273	273	TCTCTACTTCTATGCTCTT	2015	AAGAGCATAGAAGTAGAGA
siRNA 274	274	CTCTACTTCTATGCTCTTT	2016	AAAGAGCATAGAAGTAGAG
siRNA 275	275	TCTACTTCTATGCTCTTTT	2017	AAAAGAGCATAGAAGTAGA
siRNA 297	297	TCTCTCTTCAACATGTGTA	2039	TACACATGTTGAAGAGAGA
siRNA 310	310	TGTGTAGCATATGTTGCTA	2052	TAGCAACATATGCTACACA
siRNA 311	311	GTGTAGCATATGTTGCTAC	2053	GTAGCAACATATGCTACAC
siRNA 319	319	TATGTGTGCTACCAGAGACA	2061	TGTCTCTGGTAGCAACATA
siRNA 322	322	GTTGCTACCAGAGACAACT	2064	AGTTGTCTCTGGTAGCAAC
siRNA 323	323	TTGCTACCAGAGACAACTG	2065	CAGTTGTCTCTGGTAGCAA
siRNA 324	324	TGCTACCAGAGACAACTGC	2066	GCAGTTGTCTCTGGTAGCA
siRNA 329	329	CCAGAGACAACTGCTGCAT	2071	ATGCAGCAGTTGTCTCTGG
siRNA 335	335	ACAACTGCTGCATCTTAGA	2077	TCTAAGATGCAGCAGTTGT
siRNA 342	342	CTGCATCTTAGATGAAAGA	2084	TCTTTTCATCTAAGATGCAG
siRNA 343	343	TGCATCTTAGATGAAAGAT	2085	ATCTTTTCATCTAAGATGCA
siRNA 344	344	GCATCTTAGATGAAAGATT	2086	AATCTTTTCATCTAAGATGC
siRNA 347	347	TCTTAGATGAAAGATTTCGG	2089	CCGAATCTTTTCATCTAAGA
siRNA 348	348	CTTAGATGAAAGATTTCGGT	2090	ACCGAATCTTTTCATCTAAG
siRNA 349	349	TTAGATGAAAGATTTCGGTA	2091	TACCGAATCTTTTCATCTAA
siRNA 350	350	TAGATGAAAGATTTCGGTAG	2092	CTACCGAATCTTTTCATCTA
siRNA 351	351	AGATGAAAGATTTCGGTAGT	2093	ACTACCGAATCTTTTCATCT
siRNA 352	352	GATGAAAGATTTCGGTAGTT	2094	AACTACCGAATCTTTTCATC
siRNA 354	354	TGAAAGATTTCGGTAGTTAT	2096	ATAACTACCGAATCTTTTCA
siRNA 355	355	GAAAGATTTCGGTAGTTATT	2097	AATAACTACCGAATCTTTTC
siRNA 359	359	GATTTCGGTAGTTATTGTCC	2101	GGACAATAACTACCGAATC
siRNA 361	361	TTCGGTAGTTATTGTCCAA	2103	TTGGACAATAACTACCGAA
siRNA 362	362	TCGGTAGTTATTGTCCAAC	2104	GTTGGACAATAACTACCGA
siRNA 363	363	CGGTAGTTATTGTCCAAC	2105	AGTTGGACAATAACTACCG
siRNA 364	364	GGTAGTTATTGTCCAAC	2106	TAGTTGGACAATAACTACC
siRNA 365	365	GTAGTTATTGTCCAAC	2107	GTAGTTGGACAATAACTAC
siRNA 366	366	TAGTTATTGTCCAAC	2108	GGTAGTTGGACAATAACTA
siRNA 367	367	AGTTATTGTCCAAC	2109	AGGTAGTTGGACAATAACT
siRNA 369	369	TTATTGTCCAAC	2111	ACAGGTAGTTGGACAATAA
siRNA 372	372	TTGTCCAAC	2114	GCCACAGGTAGTTGGACAA
siRNA 373	373	TGTCCAAC	2115	TGCCACAGGTAGTTGGACA
siRNA 384	384	CTGTGGCATTGCAGATTTC	2126	GAAATCTGCAATGCCACAG
siRNA 386	386	GTGGCATTGCAGATTTCCT	2128	AGGAAATCTGCAATGCCAC
siRNA 392	392	TTGCAGATTTCTGTCTAC	2134	GTAGACAGGAAATCTGCAA
siRNA 397	397	GATTTCTGTCTACTTATC	2139	GATAAGTAGACAGGAAATC
siRNA 398	398	ATTTCTGTCTACTTATCA	2140	TGATAAGTAGACAGGAAAT
siRNA 399	399	TTTCTGTCTACTTATCAA	2141	TTGATAAGTAGACAGGAAA
siRNA 406	406	TCTACTTATCAAACCAAAG	2148	CTTTGGTTTGATAAGTAGA
siRNA 411	411	TTATCAAACCAAAGTAGAC	2153	GTCTACTTTGGTTTGATAA
siRNA 412	412	TATCAAACCAAAGTAGACA	2154	TGTCTACTTTGGTTTGATA
siRNA 423	423	AGTAGACAAGGATCTACAG	2165	CTGTAGATCCTTGTCTACT
siRNA 426	426	AGACAAGGATCTACAGTCT	2168	AGACTGTAGATCCTTGTCT
siRNA 432	432	GGATCTACAGTCTTTGGAA	2174	TTCCAAAGACTGTAGATCC
siRNA 434	434	ATCTACAGTCTTTGGAAGA	2176	TCTTCCAAAGACTGTAGAT
siRNA 437	437	TACAGTCTTTGGAAGACAT	2179	ATGTCTTCCAAAGACTGTA

siRNA 447	447	GGAAGACATCTTACATCAA	2189	TTGATGTAAGATGTCTTCC
siRNA 449	449	AAGACATCTTACATCAAGT	2191	ACTTGATGTAAGATGTCTT
siRNA 450	450	AGACATCTTACATCAAGTT	2192	AACTTGATGTAAGATGTCT
siRNA 493	493	CAGCTGATAAAAGCAATCC	2235	GGATTGCTTTTATCAGCTG
siRNA 494	494	AGCTGATAAAAGCAATCCA	2236	TGGATTGCTTTTATCAGCT
siRNA 497	497	TGATAAAAGCAATCCAAC	2239	AGTTGGATTGCTTTTATCA
siRNA 504	504	AGCAATCCAACCTCACTTAT	2246	ATAAGTGAGTTGGATTGCT
siRNA 505	505	GCAATCCAACCTCACTTATA	2247	TATAAGTGAGTTGGATTGC
siRNA 507	507	AATCCAACCTCACTTATAAT	2249	ATTATAAGTGAGTTGGATT
siRNA 508	508	ATCCAACCTCACTTATAATC	2250	GATTATAAGTGAGTTGGAT
siRNA 509	509	TCCAACCTCACTTATAATCC	2251	GGATTATAAGTGAGTTGGA
siRNA 510	510	CCAACCTCACTTATAATCCT	2252	AGGATTATAAGTGAGTTGG
siRNA 511	511	CAACCTCACTTATAATCCTG	2253	CAGGATTATAAGTGAGTTG
siRNA 514	514	CTCACTTATAATCCTGATG	2256	CATCAGGATTATAAGTGAG
siRNA 515	515	TCACCTTATAATCCTGATGA	2257	TCATCAGGATTATAAGTGA
siRNA 522	522	TAATCCTGATGAATCATCA	2264	TGATGATTCATCAGGATTA
siRNA 523	523	AATCCTGATGAATCATCAA	2265	TTGATGATTCATCAGGATT
siRNA 528	528	TGATGAATCATCAAAACCA	2270	TGGTTTTGATGATTCATCA
siRNA 539	539	CAAAACCAAATATGATAGA	2281	TCTATCATATTIGGTTTIG
siRNA 541	541	AAACCAAATATGATAGACG	2283	CGTCTATCATATTGGTTT
siRNA 544	544	CCAAATATGATAGACGCTG	2286	CAGCGTCTATCATATTGG
siRNA 546	546	AAATATGATAGACGCTGCT	2288	AGCAGCGTCTATCATATT
siRNA 548	548	ATATGATAGACGCTGCTAC	2290	GTAGCAGCGTCTATCATAT
siRNA 554	554	TAGACGCTGCTACTTTGAA	2296	TTCAAAGTAGCAGCGTCTA
siRNA 556	556	GACGCTGCTACTTTGAAGT	2298	ACTTCAAAGTAGCAGCGTC
siRNA 573	573	GTCCAGGAAAATGTTAGAA	2315	TTCTAACATTTTCTGGAC
siRNA 599	599	TGAAATATGAAGCATCGAT	2341	ATCGATGCTTCATATTTCA
siRNA 600	600	GAAATATGAAGCATCGATT	2342	AATCGATGCTTCATATTT
siRNA 601	601	AAATATGAAGCATCGATTT	2343	AAATCGATGCTTCATATTT
siRNA 604	604	TATGAAGCATCGATTTTAA	2346	TTAAAAATCGATGCTTCATA
siRNA 606	606	TGAAGCATCGATTTTAAACA	2348	TGTTAAAAATCGATGCTTCA
siRNA 607	607	GAAGCATCGATTTTAAACAC	2349	GTGTTAAAAATCGATGCTTC
siRNA 608	608	AAGCATCGATTTTAAACACA	2350	TGTGTTAAAAATCGATGCTT
siRNA 609	609	AGCATCGATTTTAAACACAT	2351	ATGTGTTAAAAATCGATGCT
siRNA 619	619	TTAACACATGACTCAAGTA	2361	TACTTGAGTCATGTGTAA
siRNA 624	624	ACATGACTCAAGTATTCGA	2366	TCGAATACTTGAGTCATGT
siRNA 625	625	CATGACTCAAGTATTCGAT	2367	ATCGAATACTTGAGTCATG
siRNA 633	633	AAGTATTCGATATTTGCAG	2375	CTGCAAATATCGAATACTT
siRNA 634	634	AGTATTCGATATTTGCAGG	2376	CCTGCAAATATCGAATACT
siRNA 689	689	TGAAAGAGAAGGTAGCCCA	2431	TGGGCTACCTTCTCTTTCA
siRNA 691	691	AAAGAGAAGGTAGCCAGC	2433	GCTGGGCTACCTTCTCTTT
siRNA 709	709	CTTGAAGCACAGTGCCAGG	2451	CCTGGCACTGTGCTTCAAG
siRNA 716	716	CACAGTGCCAGGAACCTTG	2458	CAAGGTTCTTGGCACTGTG
siRNA 720	720	GTGCCAGGAACCTTGCAAA	2462	TTTGCAAGGTTCTTGGCAC
siRNA 724	724	CAGGAACCTTGCAAGACA	2466	TGTCTTTGCAAGGTTCTCTG
siRNA 728	728	AACCTTGCAAGACACGGT	2470	ACCGTGTCTTTGCAAGGTT
siRNA 729	729	ACCTTGCAAGACACGGTG	2471	CACCGTGTCTTTGCAAGGT
siRNA 730	730	CCTTGCAAGACACGGTGC	2472	GCACCGTGTCTTTGCAAGG

siRNA 731	731	CTTGCAAAGACACGGTGCA	2473	TGCACCGTGTCTTTGCAAG
siRNA 732	732	TTGCAAAGACACGGTGCAA	2474	TTGCACCGTGTCTTTGCAA
siRNA 733	733	TGCAAAGACACGGTGCAAA	2475	TTTGACACCGTGTCTTTGCA
siRNA 734	734	GCAAAGACACGGTGCAAAT	2476	ATTTGCACCGTGTCTTTGCG
siRNA 736	736	AAAGACACGGTGCAAATCC	2478	GGATTTGCACCGTGTCTTTT
siRNA 748	748	CAAATCCATGATATCACTG	2490	CAGTGATATCATGGATTTG
siRNA 749	749	AAATCCATGATATCACTGG	2491	CCAGTGATATCATGGATTTT
siRNA 751	751	ATCCATGATATCACTGGGA	2493	TCCCAGTGATATCATGGAT
siRNA 752	752	TCCATGATATCACTGGGAA	2494	TTCCCAGTGATATCATGGA
siRNA 753	753	CCATGATATCACTGGGAAA	2495	TTTCCCAGTGATATCATGG
siRNA 770	770	AAGATTGTCAAGACATTGC	2512	GCAATGTCTTGACAATCTT
siRNA 778	778	CAAGACATTGCCAATAAGG	2520	CCTTATTGGCAATGTCTTG
siRNA 780	780	AGACATTGCCAATAAGGGA	2522	TCCCTTATTGGCAATGTCT
siRNA 783	783	CATTGCCAATAAGGGAGCT	2525	AGCTCCCTTATTGGCAATG
siRNA 784	784	ATTGCCAATAAGGGAGCTA	2526	TAGCTCCCTTATTGGCAAT
siRNA 785	785	TTGCCAATAAGGGAGCTAA	2527	TTAGCTCCCTTATTGGCAA
siRNA 786	786	TGCCAATAAGGGAGCTAAA	2528	TTTAGCTCCCTTATTGGCA
siRNA 791	791	ATAAGGGAGCTAAACAGAG	2533	CTCTGTTTAGCTCCCTTAT
siRNA 794	794	AGGGAGCTAAACAGAGCGG	2536	CCGCTCTGTTTAGCTCCCT
siRNA 795	795	GGGAGCTAAACAGAGCGGG	2537	CCCCTCTGTTTAGCTCCC
siRNA 796	796	GGAGCTAAACAGAGCGGGC	2538	GCCCGCTCTGTTTAGCTCC
siRNA 797	797	GAGCTAAACAGAGCGGGCT	2539	AGCCCGCTCTGTTTAGCTC
siRNA 800	800	CTAAACAGAGCGGGCTTTA	2542	TAAAGCCCGCTCTGTTTAG
siRNA 802	802	AAACAGAGCGGGCTTTACT	2544	AGTAAAGCCCGCTCTGTTT
siRNA 805	805	CAGAGCGGGCTTTACTTTA	2547	TAAAGTAAAGCCCGCTCTG
siRNA 806	806	AGAGCGGGCTTTACTTTAT	2548	ATAAAGTAAAGCCCGCTCT
siRNA 812	812	GGCTTTACTTTATTAAACC	2554	GGTTTAATAAAGTAAAGCC
siRNA 821	821	TTATTAAACCTCTGAAAGC	2563	GCTTTCAGAGGTTTAATAA
siRNA 822	822	TATTAAACCTCTGAAAGCT	2564	AGCTTTCAGAGGTTTAATA
siRNA 825	825	TAAACCTCTGAAAGCTAAC	2567	GTTAGCTTTCAGAGGTTTA
siRNA 826	826	AAACCTCTGAAAGCTAACCA	2568	GGTTAGCTTTCAGAGGTTT
siRNA 827	827	AACCTCTGAAAGCTAACCA	2569	TGGTTAGCTTTCAGAGGTT
siRNA 828	828	ACCTCTGAAAGCTAACCAAG	2570	CTGGTTAGCTTTCAGAGGT
siRNA 833	833	TGAAAGCTAACCAGCAATT	2575	AATTGCTGGTTAGCTTTCA
siRNA 841	841	AACCAGCAATTCTTAGTCT	2583	AGACTAAGAATTGCTGGTT
siRNA 844	844	CAGCAATTCTTAGTCTACT	2586	AGTAGACTAAGAATTGCTG
siRNA 850	850	TTCTTAGTCTACTGTGAAA	2592	TTTCACAGTAGACTAAGAA
siRNA 860	860	ACTGTGAAATCGATGGGTC	2602	GACCCATCGATTTCACAGT
siRNA 861	861	CTGTGAAATCGATGGGTCT	2603	AGACCCATCGATTTCACAG
siRNA 865	865	GAAATCGATGGGTCTGGAA	2607	TTCCAGACCCATCGATTTC
siRNA 866	866	AAATCGATGGGTCTGGAAA	2608	TTTCCAGACCCATCGATTTC
siRNA 877	877	TCTGGAAATGGATGGACTG	2619	CAGTCCATCCATTTCAGAA
siRNA 893	893	CTGTGTTTCAGAAGAGACT	2635	AGTCTCTTCTGAAACACAG
siRNA 894	894	TGTGTTTCAGAAGAGACTT	2636	AAGTCTCTTCTGAAACACA
siRNA 904	904	AAGAGACTTGATGGCAGTG	2646	CACTGCCATCAAGTCTCTT
siRNA 916	916	GGCAGTGTAGATTTCAAGA	2658	TCTTGAAATCTACACTGCC
siRNA 929	929	TCAAGAAAACTGGATTCA	2671	TGAATCCAGTTTTTCTTGA
siRNA 932	932	AGAAAACTGGATTCAATA	2674	TATTGAATCCAGTTTTTCT

siRNA 955	955	GAAGGATTTGGACATCTGT	2697	ACAGATGTCCAAATCCTTC
siRNA 956	956	AAGGATTTGGACATCTGTC	2698	GACAGATGTCCAAATCCTT
siRNA 963	963	TGGACATCTGTCTCCTACT	2705	AGTAGGAGACAGATGTCCA
siRNA 964	964	GGACATCTGTCTCCTACTG	2706	CAGTAGGAGACAGATGTCC
siRNA 966	966	ACATCTGTCTCCTACTGGC	2708	GCCAGTAGGAGACAGATGT
siRNA 969	969	TCTGTCTCCTACTGGCACA	2711	TGTGCCAGTAGGAGACAGA
siRNA 972	972	GTCTCCTACTGGCACAACA	2714	TGTTGTGCCAGTAGGAGAC
siRNA 973	973	TCTCCTACTGGCACAACAG	2715	CTGTTGTGCCAGTAGGAGA
siRNA 983	983	GCACAACAGAATTTTGGCT	2725	AGCCAAAATTCTGTTGTGC
siRNA 1003	1003	GGAAATGAGAAGATTCATT	2745	AATGAATCTTCTCATTTCC
siRNA 1011	1011	GAAGATTCATTTGATAAGC	2753	GCTTATCAAATGAATCTTC
siRNA 1013	1013	AGATTCATTTGATAAGCAC	2755	GTGCTTATCAAATGAATCT
siRNA 1022	1022	TGATAAGCACACAGTCTGC	2764	GCAGACTGTGTGCTTATCA
siRNA 1024	1024	ATAAGCACACAGTCTGCCA	2766	TGGCAGACTGTGTGCTTAT
siRNA 1025	1025	TAAGCACACAGTCTGCCAT	2767	ATGGCAGACTGTGTGCTTA
siRNA 1027	1027	AGCACACAGTCTGCCATCC	2769	GGATGGCAGACTGTGTGCT
siRNA 1041	1041	CATCCCATATGCATTAAGA	2783	TCTTAATGCATATGGGATG
siRNA 1046	1046	CATATGCATTAAGAGTGGA	2788	TCCACTCTTAATGCATATG
siRNA 1047	1047	ATATGCATTAAGAGTGGA	2789	TTCCACTCTTAATGCATAT
siRNA 1052	1052	CATTAAGAGTGGAAGTGA	2794	TCCAGTTCCTCTTAATG
siRNA 1060	1060	GTGGAAGTGAAGACTGGA	2802	TCCAGTCTTCCAGTCCAC
siRNA 1071	1071	AGACTGGAATGGCAGAACC	2813	GTTCTGCCATTCCAGTCT
siRNA 1079	1079	ATGGCAGAACCAGTACTGC	2821	GCAGTACTGGTCTGCCAT
siRNA 1085	1085	GAACCACTACTGCAGACTA	2827	TAGTCTGCAGTACTGGTTC
siRNA 1088	1088	CCAGTACTGCAGACTATGC	2830	GCATAGTCTGCAGTACTGG
siRNA 1089	1089	CAGTACTGCAGACTATGCC	2831	GGCATAGTCTGCAGTACTG
siRNA 1091	1091	GTAAGTGCAGACTATGCCAT	2833	ATGGCATAGTCTGCAGTAC
siRNA 1095	1095	TGCAGACTATGCCATGTT	2837	GAACATGGCATAGTCTGCA
siRNA 1110	1110	GTTCAAGGTGGGACCTGAA	2852	TTCAGGTCCCACCTTGAAC
siRNA 1111	1111	TTCAAGGTGGGACCTGAAG	2853	CTTCAGGTCCCACCTTGA
siRNA 1120	1120	GGACCTGAAGCTGACAAGT	2862	ACTTGTGAGCTTCAGGTCC
siRNA 1123	1123	CCTGAAGCTGACAAGTACC	2865	GGTACTTGTGAGCTTCAGG
siRNA 1126	1126	GAAGCTGACAAGTACCGCC	2868	GGCGGTACTTGTGAGCTTC
siRNA 1127	1127	AAGCTGACAAGTACCGCCT	2869	AGGCGGTACTTGTGAGCTT
siRNA 1128	1128	AGCTGACAAGTACCGCCTA	2870	TAGGCGGTACTTGTGAGCT
siRNA 1129	1129	GCTGACAAGTACCGCCTAA	2871	TTAGGCGGTACTTGTGAGC
siRNA 1130	1130	CTGACAAGTACCGCCTAAC	2872	GTTAGGCGGTACTTGTGAG
siRNA 1131	1131	TGACAAGTACCGCCTAACA	2873	TGTTAGGCGGTACTTGTCA
siRNA 1132	1132	GACAAGTACCGCCTAACAT	2874	ATGTTAGGCGGTACTTGTG
siRNA 1133	1133	ACAAGTACCGCCTAACATA	2875	TATGTTAGGCGGTACTTGT
siRNA 1134	1134	CAAGTACCGCCTAACATAT	2876	ATATGTTAGGCGGTACTTGT
siRNA 1135	1135	AAGTACCGCCTAACATATG	2877	CATATGTTAGGCGGTACTT
siRNA 1136	1136	AGTACCGCCTAACATATGC	2878	GCATATGTTAGGCGGTACT
siRNA 1137	1137	GTACCGCCTAACATATGCC	2879	GGCATATGTTAGGCGGTAC
siRNA 1138	1138	TACCGCCTAACATATGCCT	2880	AGGCATATGTTAGGCGGT
siRNA 1139	1139	ACCGCCTAACATATGCCTA	2881	TAGGCATATGTTAGGCGGT
siRNA 1140	1140	CCGCCTAACATATGCCTAC	2882	GTAGGCATATGTTAGGCGG
siRNA 1141	1141	CGCCTAACATATGCCTACT	2883	AGTAGGCATATGTTAGGCG

siRNA 1143	1143	CCTAACATATGCCTACTTC	2885	GAAGTAGGCATATGTTAGG
siRNA 1146	1146	AACATATGCCTACTTCGCT	2888	AGCGAAGTAGGCATATGTT
siRNA 1147	1147	ACATATGCCTACTTCGCTG	2889	CAGCGAAGTAGGCATATGT
siRNA 1148	1148	CATATGCCTACTTCGCTGG	2890	CCAGCGAAGTAGGCATATG
siRNA 1149	1149	ATATGCCTACTTCGCTGGT	2891	ACCAGCGAAGTAGGCATAT
siRNA 1151	1151	ATGCCTACTTCGCTGGTGG	2893	CCACCAGCGAAGTAGGCAT
siRNA 1174	1174	GCTGGAGATGCCTTTGATG	2916	CATCAAAGGCATCTCCAGC
siRNA 1178	1178	GAGATGCCTTTGATGGCTT	2920	AAGCCATCAAAGGCATCTC
siRNA 1182	1182	TGCCTTTGATGGCTTTGAT	2924	ATCAAAGCCATCAAAGGCA
siRNA 1197	1197	TGATTTTGGCGATGATCCT	2939	AGGATCATCGCCAAAATCA
siRNA 1198	1198	GATTTTGGCGATGATCCTA	2940	TAGGATCATCGCCAAAATC
siRNA 1203	1203	TGGCGATGATCCTAGTGAC	2945	GTCCTAGGATCATCGCCA
siRNA 1205	1205	GCGATGATCCTAGTGACAA	2947	TTGTCTAGGATCATCGC
siRNA 1206	1206	CGATGATCCTAGTGACAAG	2948	CTTGTCTAGGATCATCG
siRNA 1215	1215	TAGTGACAAGTTTTTCACA	2957	TGTGAAAACTTGTCTACTA
siRNA 1227	1227	TTTCACATCCCATAATGGC	2969	GCCATTATGGGATGTGAAA
siRNA 1236	1236	CCATAATGGCATGCAGTTC	2978	GAAGTGCATGCCATTATGG
siRNA 1242	1242	TGGCATGCAGTTCAGTACC	2984	GGTACTGAACTGCATGCCA
siRNA 1243	1243	GGCATGCAGTTCAGTACCT	2985	AGGTACTGAACTGCATGCC
siRNA 1248	1248	GCAGTTCAGTACCTGGGAC	2990	GTCCCAGGTACTGAACTGC
siRNA 1249	1249	CAGTTCAGTACCTGGGACA	2991	TGTCCCAGGTACTGAACTG
siRNA 1264	1264	GACAATGACAATGATAAGT	3006	ACTTATCATTGTCTATTGTC
siRNA 1265	1265	ACAATGACAATGATAAGTT	3007	AACTTATCATTGTCTATTGT
siRNA 1278	1278	TAAGTTTGAAGGCAACTGT	3020	ACAGTTGCCTTCAAACCTTA
siRNA 1286	1286	AAGGCAACTGTGCTGAACA	3028	TGTTTCAGCACAGTTGCCTT
siRNA 1287	1287	AGGCAACTGTGCTGAACAG	3029	CTGTTTCAGCACAGTTGCCT
siRNA 1298	1298	CTGAACAGGATGGATCTGG	3040	CCAGATCCATCCTGTTTCAG
siRNA 1304	1304	AGGATGGATCTGGTTGGTG	3046	CACCAACCAGATCCATCCT
siRNA 1311	1311	ATCTGGTTGGTGGATGAAC	3053	GTTTCATCCACCAACCAGAT
siRNA 1315	1315	GGTTGGTGGATGAACAAGT	3057	ACTTGTTCATCCACCAACC
siRNA 1319	1319	GGTGGATGAACAAGTGTC	3061	TGACACTTGTTCATCCACC
siRNA 1320	1320	GTGGATGAACAAGTGTCAC	3062	GTGACACTTGTTCATCCAC
siRNA 1323	1323	GATGAACAAGTGTCACGCT	3065	AGCGTGACACTTGTTCATC
siRNA 1324	1324	ATGAACAAGTGTCACGCTG	3066	CAGCGTGACACTTGTTCAT
siRNA 1325	1325	TGAACAAGTGTCACGCTGG	3067	CCAGCGTGACACTTGTTC
siRNA 1326	1326	GAACAAGTGTCACGCTGGC	3068	GCCAGCGTGACACTTGTTC
siRNA 1339	1339	GCTGGCCATCTCAATGGAG	3081	CTCCATTGAGATGGCCAGC
siRNA 1342	1342	GGCCATCTCAATGGAGTTT	3084	AAACTCCATTGAGATGGCC
siRNA 1344	1344	CCATCTCAATGGAGTTTAT	3086	ATAAACTCCATTGAGATGG
siRNA 1348	1348	CTCAATGGAGTTTATTACC	3090	GGTAATAAACTCCATTGAG
siRNA 1349	1349	TCAATGGAGTTTATTACCA	3091	TGGTAATAAACTCCATTGA
siRNA 1354	1354	GGAGTTTATTACCAAGGTG	3096	CACCTTGGTAATAAACTCC
siRNA 1356	1356	AGTTTATTACCAAGGTGGC	3098	GCCACCTTGGTAATAAACT
siRNA 1359	1359	TTATTACCAAGGTGGCACT	3101	AGTGCCACCTTGGTAATAA
siRNA 1362	1362	TTACCAAGGTGGCACTTAC	3104	GTAAGTGCCACCTTGGTAA
siRNA 1365	1365	CCAAGGTGGCACTTACTCA	3107	TGAGTAAGTGCCACCTTGG
siRNA 1368	1368	AGGTGGCACTTACTCAAAA	3110	TTTTGAGTAAGTGCCACCT
siRNA 1374	1374	CACTTACTCAAAAGCATCT	3116	AGATGCTTTTGGAGTAAGTG

siRNA 1383	1383	AAAAGCATCTACTCCTAAT	3125	ATTAGGAGTAGATGCTTTT
siRNA 1384	1384	AAAGCATCTACTCCTAATG	3126	CATTAGGAGTAGATGCTTT
siRNA 1385	1385	AAGCATCTACTCCTAATGG	3127	CCATTAGGAGTAGATGCTT
siRNA 1386	1386	AGCATCTACTCCTAATGGT	3128	ACCATTAGGAGTAGATGCT
siRNA 1387	1387	GCATCTACTCCTAATGGTT	3129	AACCATTAGGAGTAGATGC
siRNA 1389	1389	ATCTACTCCTAATGGTTAT	3131	ATAACCATTAGGAGTAGAT
siRNA 1390	1390	TCTACTCCTAATGGTTATG	3132	CATAACCATTAGGAGTAGA
siRNA 1391	1391	CTACTCCTAATGGTTATGA	3133	TCATAACCATTAGGAGTAG
siRNA 1394	1394	CTCCTAATGGTTATGATAA	3136	TTATCATAACCATTAGGAG
siRNA 1395	1395	TCCTAATGGTTATGATAAT	3137	ATTATCATAACCATTAGGA
siRNA 1396	1396	CCTAATGGTTATGATAATG	3138	CATTATCATAACCATTAGG
siRNA 1401	1401	TGGTTATGATAATGGCATT	3143	AATGCCATTATCATAACCA
siRNA 1404	1404	TTATGATAATGGCATTATT	3146	AATAATGCCATTATCATAA
siRNA 1409	1409	ATAATGGCATTATTTGGGC	3151	GCCCAAATAATGCCATTAT
siRNA 1410	1410	TAATGGCATTATTTGGGCC	3152	GGCCCAAATAATGCCATT
siRNA 1417	1417	ATTATTTGGGCCACTTGGA	3159	TCCAAGTGGCCCAAATAAT
siRNA 1418	1418	TTATTTGGGCCACTTGGA	3160	TTCCAAGTGGCCCAAATAA
siRNA 1419	1419	TATTTGGGCCACTTGGA	3161	TTTCCAAGTGGCCCAAATA
siRNA 1420	1420	ATTITGGGCCACTTGGA	3162	TTTTCCAAGTGGCCCAAAT
siRNA 1426	1426	GCCACTTGGA	3168	ACCGGGTTTTCCAAGTGGC
siRNA 1427	1427	CCACTTGGA	3169	CACCGGGTTTTCCAAGTGG
siRNA 1428	1428	CACTTGGA	3170	CCACCGGGTTTTCCAAGTG
siRNA 1431	1431	TTGGA	3173	ATACCACCGGGTTTTCCA
siRNA 1432	1432	TGGA	3174	AATACCACCGGGTTTTCCA
siRNA 1434	1434	GAA	3176	GGAATACCACCGGGTTTTC
siRNA 1435	1435	AAA	3177	TGGAATACCACCGGGTTTT
siRNA 1440	1440	CCGTGGTATTCCATGAAG	3182	CTTCATGGAATACCACCGG
siRNA 1461	1461	AACCACTATGAAGATAATC	3203	GATTATCTTCATAGTGGTT
siRNA 1462	1462	ACCACTATGAAGATAATCC	3204	GGATTATCTTCATAGTGGT
siRNA 1466	1466	CTATGAAGATAATCCCAT	3208	AATGGGATTATCTTCATAG
siRNA 1467	1467	TATGAAGATAATCCCATTC	3209	GAATGGGATTATCTTCATA
siRNA 1477	1477	ATCCCATTCAACAGACTCA	3219	TGAGTCTGTTGAATGGGAT
siRNA 1478	1478	TCCCATTCAACAGACTCAC	3220	GTGAGTCTGTTGAATGGGA
siRNA 1482	1482	ATTCAACAGACTCACAATT	3224	AATTGTGAGTCTGTTGAAT
siRNA 1485	1485	CAACAGACTCACAATTGGA	3227	TCCAATTGTGAGTCTGTTG
siRNA 1487	1487	ACAGACTCACAATTGGAGA	3229	TCTCCAATTGTGAGTCTGT
siRNA 1488	1488	CAGACTCACAATTGGAGAA	3230	TTCTCCAATTGTGAGTCTG
siRNA 1519	1519	CACCTGGGGGGAGCCAAAC	3261	GTTTGGCTCCCCCAGGTG
siRNA 1533	1533	CAAACAGGCTGGAGACGTT	3275	AACGTCTCCAGCCTGTTTG
siRNA 1540	1540	GCTGGAGACGTTTAAAGA	3282	TCTTTTAAACGTCTCCAGC
siRNA 1583	1583	TTAAAGGACTTTATCTGAA	3325	TTCAGATAAAGTCCTTTAA
siRNA 1588	1588	GGACTTTATCTGAACAGAG	3330	CTCTGTTTCAGATAAAGTCC
siRNA 1592	1592	TTTATCTGAACAGAGAGAT	3334	ATCTCTCTGTTTCAGATAA
siRNA 1597	1597	CTGAACAGAGAGATATAAT	3339	ATTATATCTCTCTGTTTCAG
siRNA 1615	1615	TATTTTCTTATTGGACAA	3357	TTGTCCAATAGGAAAAATA
siRNA 1617	1617	TTTTTCTTATTGGACAATG	3359	CATTGTCCAATAGGAAAAA
siRNA 1622	1622	CCTATTGGACAATGGACTT	3364	AAGTCCATTGTCCAATAGG
siRNA 1623	1623	CTATTGGACAATGGACTTG	3365	CAAGTCCATTGTCCAATAG

siRNA 1626	1626	TTGGACAATGGACTTGCAA	3368	TTGCAAGTCCATTGTCCAA
siRNA 1627	1627	TGGACAATGGACTTGCAA	3369	TTTGCAAGTCCATTGTCCA
siRNA 1647	1647	CTTCACTTCATTTTAAGAG	3389	CTCTTAAAATGAAGTGAAG
siRNA 1648	1648	TTCACCTTCATTTTAAGAGC	3390	GCTCTTAAAATGAAGTGAA
siRNA 1649	1649	TCACTTCATTTTAAGAGCA	3391	TGCTCTTAAAATGAAGTGA
siRNA 1664	1664	AGCAAAAGACCCCATGTTG	3406	CAACATGGGGTCTTTTGCT
siRNA 1672	1672	ACCCCATGTTGAAAACCTCC	3414	GGAGTTTTTCAACATGGGGT
siRNA 1678	1678	TGTTGAAAACCTCCATAACA	3420	TGTTATGGAGTTTTCACAA
siRNA 1679	1679	GTTGAAAACCTCCATAACAG	3421	CTGTTATGGAGTTTTCAC
siRNA 1680	1680	TTGAAAACCTCCATAACAGT	3422	ACTGTTATGGAGTTTTCAC
siRNA 1691	1691	ATAACAGTTTATGCTGAT	3433	ATCAGCATAAAACTGTTAT
siRNA 1696	1696	AGTTTTATGCTGATGATAA	3438	TTATCATCAGCATAAAACT
siRNA 1700	1700	TTATGCTGATGATAATTTA	3442	TAAATTATCATCAGCATAA
siRNA 1710	1710	GATAATTTATCTACATGCA	3452	TGCATGTAGATAAATTATC

[00330] The siRNAs in subset B were selected to have the following characteristics:

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

[00331] The siRNA sequences in subset B were further selected for absence of seed regions in the AS strand that are identical to a seed region of known human miRNA to yield subset C. Subset C includes 221 siRNAs whose base sequences are shown in Table 5.

Table 5: Subset C siRNAs

siRNA Name	Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 224	224	CCGGGCACTCAGACATCAT	1966	ATGATGTCTGAGTGCCCGG
siRNA 233	233	CAGACATCATGAGTTGGTC	1975	GACCAACTCATGATGTCTG
siRNA 234	234	AGACATCATGAGTTGGTCC	1976	GGACCAACTCATGATGTCT
siRNA 250	250	TCCTTGCACCCCGGAATT	1992	AATTCCGGGGGTGCAAGGA
siRNA 251	251	CCTTGCACCCCGGAATTT	1993	AAATTCCGGGGGTGCAAGG
siRNA 253	253	TTGCACCCCGGAATTTAA	1995	TTAAATTCCGGGGGTGCAA
siRNA 254	254	TGCACCCCGGAATTTAAT	1996	ATTAAATTCCGGGGGTGCA
siRNA 255	255	GCACCCCGGAATTTAATT	1997	AATTAAATTCCGGGGGTGC
siRNA 258	258	CCCCCGGAATTTAATTCTC	2000	GAGAATTAAATTCCGGGGG
siRNA 261	261	CCGGAATTTAATTCTCTAC	2003	GTAGAGAATTAAATTCCGG
siRNA 269	269	TAATTCTCTACTTCTATGC	2011	GCATAGAAGTAGAGAATTA
siRNA 274	274	CTCTACTTCTATGCTCTTT	2016	AAAGAGCATAGAAGTAGAG
siRNA 310	310	TGTGTAGCATATGTTGCTA	2052	TAGCAACATATGCTACACA
siRNA 323	323	TTGCTACCAGAGACAACCTG	2065	CAGTTGTCTCTGGTAGCAA
siRNA 324	324	TGCTACCAGAGACAACCTGC	2066	GCAGTTGTCTCTGGTAGCA
siRNA 335	335	ACAAGTCTGCATCTTAGA	2077	TCTAAGATGCAGCAGTTGT
siRNA 342	342	CTGCATCTTAGATGAAAGA	2084	TCTTTTCATCTAAGATGCAG
siRNA 343	343	TGCATCTTAGATGAAAGAT	2085	ATCTTTTCATCTAAGATGCA

siRNA 344	344	GCATCTTAGATGAAAGATT	2086	AATCTTTCATCTAAGATGC
siRNA 347	347	TCTTAGATGAAAGATTCCGG	2089	CCGAATCTTTCATCTAAGA
siRNA 348	348	CTTAGATGAAAGATTCCGGT	2090	ACCGAATCTTTCATCTAAG
siRNA 349	349	TTAGATGAAAGATTCCGGTA	2091	TACCGAATCTTTCATCTAA
siRNA 350	350	TAGATGAAAGATTCCGGTAG	2092	CTACCGAATCTTTCATCTA
siRNA 351	351	AGATGAAAGATTCCGGTAGT	2093	ACTACCGAATCTTTCATCT
siRNA 352	352	GATGAAAGATTCCGGTAGTT	2094	AACTACCGAATCTTTCATC
siRNA 354	354	TGAAAGATTCCGGTAGTTAT	2096	ATAACTACCGAATCTTTC
siRNA 355	355	GAAAGATTCCGGTAGTTATT	2097	AATAACTACCGAATCTTTC
siRNA 359	359	GATTCGGTAGTTATTGTCC	2101	GGACAATAACTACCGAATC
siRNA 363	363	CGGTAGTTATTGTCCAAC	2105	AGTTGGACAATAACTACCG
siRNA 365	365	GTAGTTATTGTCCAAC	2107	GTAGTTGGACAATAACTAC
siRNA 367	367	AGTTATTGTCCAAC	2109	AGGTAGTTGGACAATAACT
siRNA 369	369	TTATTGTCCAAC	2111	ACAGGTAGTTGGACAATAA
siRNA 372	372	TTGTCCAAC	2114	GCCACAGGTAGTTGGACAA
siRNA 373	373	TGTCCAAC	2115	TGCCACAGGTAGTTGGACA
siRNA 384	384	CTGTGGCATTGCAGATTT	2126	GAAATCTGCAATGCCACAG
siRNA 392	392	TTGCAGATTTCTGTCTAC	2134	GTAGACAGGAAATCTGCAA
siRNA 397	397	GATTTCCIGTCTACTTATC	2139	GATAAGTAGACAGGAAATC
siRNA 398	398	ATTTCCTGTCTACTTATCA	2140	TGATAAGTAGACAGGAAAT
siRNA 406	406	TCTACTTATCAAACCAAAG	2148	CTTTGGTTTGATAAGTAGA
siRNA 411	411	TTATCAAACCAAAGTAGAC	2153	GTCTACTTTGGTTTGATAA
siRNA 423	423	AGTAGACAAGGATCTACAG	2165	CTGTAGATCCTTGTCTACT
siRNA 426	426	AGACAAGGATCTACAGTCT	2168	AGACTGTAGATCCTTGTCT
siRNA 432	432	GGATCTACAGTCTTTGGAA	2174	TTCCAAAGACTGTAGATCC
siRNA 434	434	ATCTACAGTCTTTGGGAAGA	2176	TCTTCCAAAGACTGTAGAT
siRNA 447	447	GGAAGACATCTTACATCAA	2189	TTGATGTAAGATGTCTTCC
siRNA 449	449	AAGACATCTTACATCAAGT	2191	ACTTGATGTAAGATGTCTT
siRNA 450	450	AGACATCTTACATCAAGTT	2192	AACTTGATGTAAGATGTCT
siRNA 493	493	CAGCTGATAAAAGCAATCC	2235	GGATTGCTTTTATCAGCTG
siRNA 494	494	AGCTGATAAAAGCAATCCA	2236	TGGATTGCTTTTATCAGCT
siRNA 497	497	TGATAAAAGCAATCCAAC	2239	AGTTGGATTGCTTTTATCA
siRNA 504	504	AGCAATCCAAC	2246	ATAAGTGAGTTGGATTGCT
siRNA 505	505	GCAATCCAAC	2247	TATAAGTGAGTTGGATTGC
siRNA 507	507	AATCCAAC	2249	ATTATAAGTGAGTTGGATT
siRNA 508	508	ATCCAAC	2250	GATTATAAGTGAGTTGGAT
siRNA 509	509	TCCAAC	2251	GGATTATAAGTGAGTTGGA
siRNA 510	510	CCAAC	2252	AGGATTATAAGTGAGTTGG
siRNA 514	514	CTCACTTATAATCCTGATG	2256	CATCAGGATTATAAGTGAG
siRNA 515	515	TCACCTTATAATCCTGATGA	2257	TCATCAGGATTATAAGTGAG
siRNA 523	523	AATCCTGATGAATCATCAA	2265	TTGATGATTCATCAGGATT
siRNA 528	528	TGATGAATCATCAAAACCA	2270	TGGTTTTGATGATTCATCA
siRNA 539	539	CAAAACCAATATGATAGA	2281	TCTATCATATTTGGTTTTG
siRNA 544	544	CCAAATATGATAGACGCTG	2286	CAGCGTCTATCATATTTGG
siRNA 546	546	AAATATGATAGACGCTGCT	2288	AGCAGCGTCTATCATATTT
siRNA 554	554	TAGACGCTGCTACTTTGAA	2296	TTCAAAGTAGCAGCGTCTA
siRNA 573	573	GTCCAGGAAAATGTTAGAA	2315	TTCTAACATTTTCTGGAC
siRNA 599	599	TGAAATATGAAGCATCGAT	2341	ATCGATGCTTCATATTTCA

siRNA 600	600	GAAATATGAAGCATCGATT	2342	AATCGATGCTTCATATTTTC
siRNA 601	601	AAATATGAAGCATCGATTT	2343	AAATCGATGCTTCATATTT
siRNA 604	604	TATGAAGCATCGATTTTAA	2346	TTAAAATCGATGCTTCATA
siRNA 606	606	TGAAGCATCGATTTTAAACA	2348	TGTTAAAATCGATGCTTCA
siRNA 609	609	AGCATCGATTTTAAACACAT	2351	ATGTGTTAAAATCGATGCT
siRNA 619	619	TTAACACATGACTCAAGTA	2361	TACTTGAGTCATGTGTTAA
siRNA 624	624	ACATGACTCAAGTATTCGA	2366	TCGAATACTTGAGTCATGT
siRNA 625	625	CATGACTCAAGTATTCGAT	2367	ATCGAATACTTGAGTCATG
siRNA 661	661	AATTCAAATAATCAAAAGA	2403	TCTTTTGATTATTTGAATT
siRNA 716	716	CACAGTGCCAGGAACCTTG	2458	CAAGGTTCTGCGCACTGTG
siRNA 720	720	GTGCCAGGAACCTTGCAAA	2462	TTTGCAAGGTTCTGCGCAC
siRNA 728	728	AACCTTGCAAAGACACGGT	2470	ACCGTGTCTTTGCAAGGTT
siRNA 729	729	ACCTTGCAAAGACACGGTG	2471	CACCGTGTCTTTGCAAGGT
siRNA 730	730	CCTTGCAAAGACACGGTGC	2472	GCACCGTGTCTTTGCAAGG
siRNA 731	731	CTTGCAAAGACACGGTGCA	2473	TGCACCGTGTCTTTGCAAG
siRNA 733	733	TGCAAAGACACGGTGCAAA	2475	TTTGACCGTGTCTTTGCA
siRNA 736	736	AAAGACACGGTGCAAAATCC	2478	GGATTTGCACCGTGTCTTT
siRNA 751	751	ATCCATGATATCACTGGGA	2493	TCCCAGTGATATCATGGAT
siRNA 753	753	CCATGATATCACTGGGAAA	2495	TTTCCCAGTGATATCATGG
siRNA 770	770	AAGATTGTCAAGACATTGC	2512	GCAATGTCTTGACAATCTT
siRNA 778	778	CAAGACATTGCCAATAAGG	2520	CCTTATTGGCAATGTCTTG
siRNA 780	780	AGACATTGCCAATAAGGGA	2522	TCCCTTATTGGCAATGTCT
siRNA 784	784	ATTGCCAATAAGGGAGCTA	2526	TAGCTCCCTTATTGGCAAT
siRNA 785	785	TTGCCAATAAGGGAGCTAA	2527	TTAGCTCCCTTATTGGCAA
siRNA 786	786	TGCCAATAAGGGAGCTAAA	2528	TTTAGCTCCCTTATTGGCA
siRNA 791	791	ATAAGGGAGCTAAACAGAG	2533	CTCTGTTTAGCTCCCTTAT
siRNA 795	795	GGGAGCTAAACAGAGCGGG	2537	CCCGCTCTGTTTAGCTCCC
siRNA 796	796	GGAGCTAAACAGAGCGGGC	2538	GCCCGCTCTGTTTAGCTCC
siRNA 800	800	CTAAACAGAGCGGGCTTTA	2542	TAAAGCCCCTCTGTTTAG
siRNA 802	802	AAACAGAGCGGGCTTTACT	2544	AGTAAAGCCCCTCTGTTT
siRNA 806	806	AGAGCGGGCTTTACTTTAT	2548	ATAAAGTAAAGCCCCTCT
siRNA 812	812	GGCTTTACTTTATTAAACC	2554	GGTTTAATAAAGTAAAGCC
siRNA 821	821	TTATTAAACCTCTGAAAGC	2563	GCTTTCAGAGGTTTAATAA
siRNA 825	825	TAAACCTCTGAAAGCTAAC	2567	GTTAGCTTTCAGAGGTTTA
siRNA 826	826	AAACCTCTGAAAGCTAACC	2568	GGTTAGCTTTCAGAGGTTT
siRNA 827	827	AACCTCTGAAAGCTAACCA	2569	TGGTTAGCTTTCAGAGGTT
siRNA 833	833	TGAAAGCTAACCAGCAATT	2575	AATTGCTGGTTAGCTTTCA
siRNA 844	844	CAGCAATTCTTAGTCTACT	2586	AGTAGACTAAGAATTGCTG
siRNA 850	850	TTCTTAGTCTACTGTGAAA	2592	TTTCACAGTAGACTAAGAA
siRNA 877	877	TCTGGAAATGGATGGACTG	2619	CAGTCCATCCATTTCCAGA
siRNA 894	894	TGTGTTTCAGAAGAGACTT	2636	AAGTCTCTTCTGAAACACA
siRNA 904	904	AAGAGACTTGATGGCAGTG	2646	CACTGCCATCAAGTCTCTT
siRNA 929	929	TCAAGAAAACTGGATTCA	2671	TGAATCCAGTTTTTCTTGA
siRNA 932	932	AGAAAAACTGGATTCAATA	2674	TATTGAATCCAGTTTTTCT
siRNA 964	964	GGACATCTGTCTCCTACTG	2706	CAGTAGGAGACAGATGTCC
siRNA 972	972	GTCTCCTACTGGCACAACA	2714	TGTTGTGCCAGTAGGAGAC
siRNA 973	973	TCTCCTACTGGCACAACAG	2715	CTGTTGTGCCAGTAGGAGA
siRNA 983	983	GCACAACAGAATTTGGCT	2725	AGCCAAAATCTGTTGTGC

siRNA 1003	1003	GGAAATGAGAAGATTCATT	2745	AATGAATCTTCTCATTTCC
siRNA 1011	1011	GAAGATTCATTTGATAAGC	2753	GCTTATCAAATGAATCTTC
siRNA 1013	1013	AGATTCATTTGATAAGCAC	2755	GTGCTTATCAAATGAATCT
siRNA 1024	1024	ATAAGCACACAGTCTGCCA	2766	TGGCAGACTGTGTGCTTAT
siRNA 1027	1027	AGCACACAGTCTGCCATCC	2769	GGATGGCAGACTGTGTGCT
siRNA 1041	1041	CATCCCATATGCATTAAGA	2783	TCTTAATGCATATGGGATG
siRNA 1052	1052	CATTAAGAGTGGAAGTGGG	2794	TCCAGTTCCACTCTTAATG
siRNA 1060	1060	GTGGAAGTGGGAACTGGA	2802	TCCAGTCTTCCAGTTCCAC
siRNA 1071	1071	AGACTGGAATGGCAGAACC	2813	GGTTCTGCCATTCCAGTCT
siRNA 1079	1079	ATGGCAGAACCAGTACTGC	2821	GCAGTACTGGTTCTGCCAT
siRNA 1085	1085	GAACCAGTACTGCAGACTA	2827	TAGTCTGCAGTACTGGTTC
siRNA 1088	1088	CCAGTACTGCAGACTATGC	2830	GCATAGTCTGCAGTACTGG
siRNA 1089	1089	CAGTACTGCAGACTATGCC	2831	GGCATAGTCTGCAGTACTG
siRNA 1095	1095	TGCAGACTATGCCATGTTT	2837	GAACATGGCATAGTCTGCA
siRNA 1111	1111	TTCAAGGTGGGACCTGAAG	2853	CTTCAGGTCCACCTTGAA
siRNA 1123	1123	CCTGAAGCTGACAAGTACC	2865	GGTACTTGTGAGCTTCAGG
siRNA 1126	1126	GAAGCTGACAAGTACCGCC	2868	GGCGGTACTTGTGAGCTTC
siRNA 1127	1127	AAGCTGACAAGTACCGCCT	2869	AGGCGGTACTTGTGAGCTT
siRNA 1128	1128	AGCTGACAAGTACCGCCTA	2870	TAGGCGGTACTTGTGAGCT
siRNA 1129	1129	GCTGACAAGTACCGCCTAA	2871	TTAGGCGGTACTTGTGAGC
siRNA 1130	1130	CTGACAAGTACCGCCTAAC	2872	GTTAGGCGGTACTTGTGAG
siRNA 1132	1132	GACAAGTACCGCCTAACAT	2874	ATGTTAGGCGGTACTTGTG
siRNA 1133	1133	ACAAGTACCGCCTAACATA	2875	TATGTTAGGCGGTACTTGT
siRNA 1134	1134	CAAGTACCGCCTAACATAT	2876	ATATGTTAGGCGGTACTTG
siRNA 1135	1135	AAGTACCGCCTAACATATG	2877	CATATGTTAGGCGGTACTT
siRNA 1136	1136	AGTACCGCCTAACATATGC	2878	GCATATGTTAGGCGGTACT
siRNA 1137	1137	GTACCGCCTAACATATGCC	2879	GGCATATGTTAGGCGGTAC
siRNA 1138	1138	TACCGCCTAACATATGCCT	2880	AGGCATATGTTAGGCGGTA
siRNA 1139	1139	ACCGCCTAACATATGCCTA	2881	TAGGCATATGTTAGGCGGT
siRNA 1146	1146	AACATATGCCTACTTCGCT	2888	AGCGAAGTAGGCATATGTT
siRNA 1147	1147	ACATATGCCTACTTCGCTG	2889	CAGCGAAGTAGGCATATGT
siRNA 1148	1148	CATATGCCTACTTCGCTGG	2890	CCAGCGAAGTAGGCATATG
siRNA 1174	1174	GCTGGAGATGCCTTTGATG	2916	CATCAAAGGCATCTCCAGC
siRNA 1178	1178	GAGATGCCTTTGATGGCTT	2920	AAGCCATCAAAGGCATCTC
siRNA 1182	1182	TGCCTTTGATGGCTTTGAT	2924	ATCAAAGGCATCAAAGGCA
siRNA 1197	1197	TGATTTTGGCGATGATCCT	2939	AGGATCATCGCCAAAATCA
siRNA 1203	1203	TGGCGATGATCCTAGTGAC	2945	GTCAGTACTAGGATCATCGCA
siRNA 1205	1205	GCGATGATCCTAGTGACAA	2947	TTGTCACTAGGATCATCGC
siRNA 1206	1206	CGATGATCCTAGTGACAAG	2948	CTTGTCACTAGGATCATCG
siRNA 1215	1215	TAGTGACAAGTTTTTACACA	2957	TGTGAAAACTTGTCACTA
siRNA 1236	1236	CCATAATGGCATGCAGTTC	2978	GAAGTGCATGCCATTATGG
siRNA 1242	1242	TGGCATGCAGTTCAGTACC	2984	GGTACTGAACTGCATGCCA
siRNA 1243	1243	GGCATGCAGTTCAGTACCT	2985	AGGTACTGAACTGCATGCC
siRNA 1264	1264	GACAATGACAATGATAAGT	3006	ACTTATCATTGTCAATTGTC
siRNA 1265	1265	ACAATGACAATGATAAGTT	3007	AAGTATCATTGTCAATTGT
siRNA 1278	1278	TAAGTTTGAAGGCAACTGT	3020	ACAGTTGCCTTCAAACCTTA
siRNA 1286	1286	AAGGCAACTGTGCTGAACA	3028	TGTTTCAGCACAGTTGCCTT
siRNA 1287	1287	AGGCAACTGTGCTGAACAG	3029	CTGTTTCAGCACAGTTGCCT

siRNA 1304	1304	AGGATGGATCTGGTTGGTG	3046	CACCAACCAGATCCATCCT
siRNA 1311	1311	ATCTGGTTGGTGGATGAAC	3053	GTTTCATCCACCAACCAGAT
siRNA 1315	1315	GGTTGGTGGATGAACAAGT	3057	ACTTGTTTCATCCACCAACC
siRNA 1320	1320	GTGGATGAACAAGTGTAC	3062	GTGACACTTGTTTCATCCAC
siRNA 1323	1323	GATGAACAAGTGTACGCT	3065	AGCGTGACACTTGTTTCATC
siRNA 1324	1324	ATGAACAAGTGTACGCTG	3066	CAGCGTGACACTTGTTTCAT
siRNA 1325	1325	TGAACAAGTGTACGCTGG	3067	CCAGCGTGACACTTGTTTCA
siRNA 1339	1339	GCTGGCCATCTCAATGGAG	3081	CTCCATTGAGATGGCCAGC
siRNA 1342	1342	GGCCATCTCAATGGAGTTT	3084	AAACTCCATTGAGATGGCC
siRNA 1344	1344	CCATCTCAATGGAGTTTAT	3086	ATAAACTCCATTGAGATGG
siRNA 1348	1348	CTCAATGGAGTTTATTACC	3090	GGTAATAAACTCCATTGAG
siRNA 1349	1349	TCAATGGAGTTTATTACCA	3091	TGGTAATAAACTCCATTGA
siRNA 1356	1356	AGTTTATTACCAAGGTGGC	3098	GCCACCTTGGTAATAAACT
siRNA 1362	1362	TTACCAAGGTGGCACTTAC	3104	GTAAGTGCCACCTTGGTAA
siRNA 1365	1365	CCAAGGTGGCACTTACTCA	3107	TGAGTAAGTGCCACCTTGG
siRNA 1374	1374	CACTTACTCAAAAGCATCT	3116	AGATGCTTTTGAGTAAGTG
siRNA 1384	1384	AAAGCATCTACTCCTAATG	3126	CATTAGGAGTAGATGCTTT
siRNA 1385	1385	AAGCATCTACTCCTAATGG	3127	CCATTAGGAGTAGATGCTT
siRNA 1389	1389	ATCTACTCCTAATGGTTAT	3131	ATAACCATTAGGAGTAGAT
siRNA 1390	1390	TCTACTCCTAATGGTTATG	3132	CATAACCATTAGGAGTAGA
siRNA 1391	1391	CTACTCCTAATGGTTATGA	3133	TCATAACCATTAGGAGTAG
siRNA 1394	1394	CTCCTAATGGTTATGATAA	3136	TTATCATAACCATTAGGAG
siRNA 1396	1396	CCTAATGGTTATGATAATG	3138	CATTATCATAACCATTAGG
siRNA 1401	1401	TGGTTATGATAATGGCATT	3143	AATGCCATTATCATAACCA
siRNA 1404	1404	TTATGATAATGGCATTATT	3146	AATAATGCCATTATCATAA
siRNA 1410	1410	TAATGGCATTATTTGGGCC	3152	GGCCCAAATAATGCCATTA
siRNA 1418	1418	TTATTTGGGCCACTTGGAA	3160	TTCCAAGTGGCCCAAATAA
siRNA 1419	1419	TATTTGGGCCACTTGGAAA	3161	TTTCCAAGTGGCCCAAATA
siRNA 1420	1420	ATTTGGGCCACTTGGAAAA	3162	TTTTCCAAGTGGCCCAAAT
siRNA 1426	1426	GCCACTTGGAAAACCCGGT	3168	ACCGGGTTTTTCCAAGTGGC
siRNA 1431	1431	TTGGAAAACCCGGTGGTAT	3173	ATACCACCGGGTTTTCCAA
siRNA 1432	1432	TGGAAAACCCGGTGGTATT	3174	AATACCACCGGGTTTTCCA
siRNA 1434	1434	GAAAACCCGGTGGTATTCC	3176	GGAATACCACCGGGTTTTTC
siRNA 1435	1435	AAAACCCGGTGGTATTCCA	3177	TGGAATACCACCGGGTTTTT
siRNA 1440	1440	CCGGTGGTATTCCATGAAG	3182	CTTCATGGAATACCACCGG
siRNA 1461	1461	AACCACTATGAAGATAATC	3203	GATTATCTTCATAGTGGTT
siRNA 1462	1462	ACCACTATGAAGATAATCC	3204	GGATTATCTTCATAGTGGT
siRNA 1482	1482	ATTCAACAGACTCACAATT	3224	AATTGTGAGTCTGTTGAAT
siRNA 1485	1485	CAACAGACTCACAATTGGA	3227	TCCAATTGTGAGTCTGTTG
siRNA 1519	1519	CACCTGGGGGGAGCCAAAC	3261	GTTTGGCTCCCCCAGGTG
siRNA 1533	1533	CAAACAGGCTGGAGACGTT	3275	AACGTCTCCAGCCTGTTTG
siRNA 1540	1540	GCTGGAGACGTTTAAAAGA	3282	TCTTTTAAACGTCTCCAGC
siRNA 1588	1588	GGACTTTATCTGAACAGAG	3330	CTCTGTTTCAGATAAAGTCC
siRNA 1617	1617	TTTTTCCTATTGGACAATG	3359	CATTGTCCAATAGGAAAAA
siRNA 1622	1622	CCTATTGGACAATGGACTT	3364	AAGTCCATTGTCCAATAGG
siRNA 1623	1623	CTATTGGACAATGGACTTG	3365	CAAGTCCATTGTCCAATAG
siRNA 1626	1626	TTGGACAATGGACTTGCAA	3368	TTGCAAGTCCATTGTCCAA
siRNA 1627	1627	TGGACAATGGACTTGCAAA	3369	TTTGCAAGTCCATTGTCCA

siRNA 1647	1647	CTTCACTTCATTTTAAGAG	3389	CTCTTAAAATGAAGTGAAG
siRNA 1648	1648	TTCACCTTCATTTTAAGAGC	3390	GCTCTTAAAATGAAGTGAA
siRNA 1649	1649	TCACTTCATTTTAAGAGCA	3391	TGCTCTTAAAATGAAGTGA
siRNA 1664	1664	AGCAAAAGACCCCATGTTG	3406	CAACATGGGGTCTTTTGCT
siRNA 1672	1672	ACCCCATGTTGAAAACCTCC	3414	GGAGTTTTCAACATGGGGT
siRNA 1678	1678	TGTTGAAAACCTCCATAACA	3420	TGTTATGGAGTTTTCAACA
siRNA 1679	1679	GTTGAAAACCTCCATAACAG	3421	CTGTTATGGAGTTTTCAAC
siRNA 1680	1680	TTGAAAACCTCCATAACAGT	3422	ACTGTTATGGAGTTTTCAA
siRNA 1696	1696	AGTTTTATGCTGATGATAA	3438	TTATCATCAGCATAAAACCT
siRNA 1700	1700	TTATGCTGATGATAATTTA	3442	TAAATTATCATCAGCATAA
siRNA 1710	1710	GATAATTTATCTACATGCA	3452	TGCATGTAGATAAATTATC

[00332] The siRNAs in subset C have the following characteristics:

- Cross-reactivity: With 19mer in human FGG mRNA, with 17mer/19mer in NHP FGG
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤ 30 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF $\geq 1\%$ (pos. 2-18)

[00333] The siRNA sequences in subset C were also selected for absence of seed regions in the AS or S strands that are identical to a seed region of known human miRNA to yield subset D. Subset D includes 147 siRNAs whose base sequences are shown in Table 6.

Table 6. Subset D siRNAs

siRNA Name	Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 233	233	CAGACATCATGAGTTGGTC	1975	GACCAACTCATGATGTCTG
siRNA 251	251	CCTTGCACCCCGGAATTT	1993	AAATTCCGGGGGTGCAAGG
siRNA 254	254	TGCACCCCGGAATTTAAT	1996	ATTAAATTCCGGGGGTGCA
siRNA 255	255	GCACCCCGGAATTTAATT	1997	AATTAAATTCCGGGGGTGC
siRNA 261	261	CCGGAATTTAATTCTCTAC	2003	GTAGAGAATTAAATTCCGG
siRNA 274	274	CTCTACTTCTATGCTCTTT	2016	AAAGAGCATAGAAGTAGAG
siRNA 310	310	TGTGTAGCATATGTTGCTA	2052	TAGCAACATATGCTACACA
siRNA 324	324	TGCTACCAGAGACAACCTGC	2066	GCAGTTGTCTCTGGTAGCA
siRNA 335	335	ACAACCTGCTGCATCTTAGA	2077	TCTAAGATGCAGCAGTTGT
siRNA 342	342	CTGCATCTTAGATGAAAGA	2084	TCTTTCATCTAAGATGCAG
siRNA 343	343	TGCATCTTAGATGAAAGAT	2085	ATCTTTCATCTAAGATGCA
siRNA 344	344	GCATCTTAGATGAAAGATT	2086	AATCTTTCATCTAAGATGC
siRNA 347	347	TCTTAGATGAAAGATTCCGG	2089	CCGAATCTTTCATCTAAGA
siRNA 349	349	TTAGATGAAAGATTCCGGTA	2091	TACCGAATCTTTCATCTAA
siRNA 350	350	TAGATGAAAGATTCCGGTAG	2092	CTACCGAATCTTTCATCTA
siRNA 351	351	AGATGAAAGATTCCGGTAGT	2093	ACTACCGAATCTTTCATCT
siRNA 352	352	GATGAAAGATTCCGGTAGTT	2094	AACTACCGAATCTTTCATC
siRNA 354	354	TGAAAGATTCCGGTAGTTAT	2096	ATAACTACCGAATCTTTCA

siRNA 355	355	GAAAGATTCGGTAGTTATT	2097	AATAACTACCGAATCTTTC
siRNA 359	359	GATTCGGTAGTTATTGTCC	2101	GGACAATAACTACCGAATC
siRNA 363	363	CGGTAGTTATTGTCCAAC	2105	AGTTGGACAATAACTACCG
siRNA 365	365	GTAGTTATTGTCCAAC	2107	GAGTTGGACAATAACTAC
siRNA 367	367	AGTTATTGTCCAAC	2109	AGGTAGTTGGACAATAACT
siRNA 373	373	TGTCCAAC	2115	TGCCACAGGTAGTTGGACA
siRNA 397	397	GATTCCTGTCTACTTATC	2139	GATAAGTAGACAGGAAATC
siRNA 398	398	ATTCCTGTCTACTTATCA	2140	TGATAAGTAGACAGGAAAT
siRNA 411	411	TTATCAAACCAAAGTAGAC	2153	GTCTACTTTGGTTTGATAA
siRNA 423	423	AGTAGACAAGGATCTACAG	2165	CTGTAGATCCTTGTCTACT
siRNA 426	426	AGACAAGGATCTACAGTCT	2168	AGACTGTAGATCCTTGTCT
siRNA 432	432	GGATCTACAGTCTTTGGAA	2174	TTCCAAAGACTGTAGATCC
siRNA 434	434	ATCTACAGTCTTTGGAAGA	2176	TCTTCCAAAGACTGTAGAT
siRNA 447	447	GGAAGACATCTTACATCAA	2189	TTGATGTAAGATGTCTTCC
siRNA 449	449	AAGACATCTTACATCAAGT	2191	ACTTGATGTAAGATGTCTT
siRNA 493	493	CAGCTGATAAAAGCAATCC	2235	GGATTGCTTTTATCAGCTG
siRNA 497	497	TGATAAAAGCAATCCAAC	2239	AGTTGGATTGCTTTTATCA
siRNA 504	504	AGCAATCCAAC	2246	ATAAGTGAGTTGGATTGCT
siRNA 505	505	GCAATCCAAC	2247	TATAAGTGAGTTGGATTGC
siRNA 507	507	AATCCAAC	2249	ATTATAAGTGAGTTGGATT
siRNA 508	508	ATCCAAC	2250	GATTATAAGTGAGTTGGAT
siRNA 509	509	TCCAAC	2251	GGATTATAAGTGAGTTGGA
siRNA 510	510	CCAAC	2252	AGGATTATAAGTGAGTTGG
siRNA 514	514	CTACTTATAATCCTGATG	2256	CATCAGGATTATAAGTGAG
siRNA 515	515	TCACTTATAATCCTGATGA	2257	TCATCAGGATTATAAGTGGA
siRNA 523	523	AATCCTGATGAATCATCAA	2265	TTGATGATTCATCAGGATT
siRNA 528	528	TGATGAATCATCAAAACCA	2270	TGGTTTTGATGATTCATCA
siRNA 544	544	CCAAATATGATAGACGCTG	2286	CAGCGTCTATCATATTTGG
siRNA 554	554	TAGACGCTGCTACTTTGAA	2296	TTCAAAGTAGCAGCGTCTA
siRNA 573	573	GTCCAGGAAAATGTTAGAA	2315	TTCTAACATTTTCTGGAC
siRNA 599	599	TGAAATATGAAGCATCGAT	2341	ATCGATGCTTCATATTTCA
siRNA 600	600	GAAATATGAAGCATCGATT	2342	AATCGATGCTTCATATTTTC
siRNA 604	604	TATGAAGCATCGATTTTAA	2346	TTAAAATCGATGCTTCATA
siRNA 606	606	TGAAGCATCGATTTTAAACA	2348	TGTTAAAATCGATGCTTCA
siRNA 609	609	AGCATCGATTTTAAACACAT	2351	ATGTGTTAAAATCGATGCT
siRNA 619	619	TTAACACATGACTCAAGTA	2361	TACTTGAGTCATGTGTTAA
siRNA 624	624	ACATGACTCAAGTATTCGA	2366	TCGAATACTTGAGTCATGT
siRNA 625	625	CATGACTCAAGTATTCGAT	2367	ATCGAATACTTGAGTCATG
siRNA 716	716	CACAGTGCCAGGAACCTTG	2458	CAAGGTTCTTGGCACTGTG
siRNA 730	730	CCTTGCAAAGACACGGTGC	2472	GCACCGTGTCTTTGCAAGG
siRNA 731	731	CTTGCAAAGACACGGTGCA	2473	TGCACCGTGTCTTTGCAAG
siRNA 733	733	TGCAAAGACACGGTGCAAA	2475	TTTGACCGTGTCTTTGCA
siRNA 753	753	CCATGATATCACTGGGAAA	2495	TTTCCAGTGATATCATGG
siRNA 770	770	AAGATTGTCAAGACATTGC	2512	GCAATGTCTTGACAATCTT
siRNA 780	780	AGACATTGCCAATAAGGGA	2522	TCCCTTATTGGCAATGTCT
siRNA 786	786	TGCCAATAAGGGAGCTAAA	2528	TTAGCTCCCTTATTGGCA
siRNA 800	800	CTAAACAGAGCGGGCTTTA	2542	TAAAGCCCGCTCTGTTTAG
siRNA 802	802	AAACAGAGCGGGCTTTACT	2544	AGTAAAGCCCGCTCTGTTT

siRNA 806	806	AGAGCGGGCTTTACTTTAT	2548	ATAAAGTAAAGCCCCGCTCT
siRNA 812	812	GGCTTTACTTTATTAAACC	2554	GGTTTAATAAAGTAAAGCC
siRNA 825	825	TAAACCTCTGAAAGCTAAC	2567	GTTAGCTTTCAGAGGTTTA
siRNA 833	833	TGAAAGCTAACCAGCAATT	2575	AATTGCTGGTTAGCTTTCA
siRNA 850	850	TTCTTAGTCTACTGTGAAA	2592	TTTCACAGTAGACTAAGAA
siRNA 894	894	TGTGTTTCAGAAGAGACTT	2636	AAGTCTCTTCTGAAACACA
siRNA 904	904	AAGAGACTTGATGGCAGTG	2646	CACTGCCATCAAGTCTCTT
siRNA 929	929	TCAAGAAAACTGGATTCA	2671	TGAATCCAGTTTTTCTTGA
siRNA 932	932	AGAAAAACTGGATTCAATA	2674	TATTGAATCCAGTTTTTCT
siRNA 973	973	TCTCCTACTGGCACAACAG	2715	CTGTTGTGCCAGTAGGAGA
siRNA 1003	1003	GGAAATGAGAAGATTTCATT	2745	AATGAATCTTCTCATTTCC
siRNA 1011	1011	GAAGATTTCATTTGATAAGC	2753	GCTTATCAAATGAATCTTC
siRNA 1013	1013	AGATTTCATTTGATAAGCAC	2755	GTGCTTATCAAATGAATCT
siRNA 1052	1052	CATTAAGAGTGGAAGTGGG	2794	TCCAGTCCACTCTTAATG
siRNA 1060	1060	GTGGAAGTGGGAGTGGG	2802	TCCAGTCTCCAGTCCAC
siRNA 1071	1071	AGACTGGAATGGCAGAACC	2813	GGTTCGCCATTCCAGTCT
siRNA 1085	1085	GAACCACTACTGCAGACTA	2827	TAGTCTGCAGTACTGGTTC
siRNA 1088	1088	CCAGTACTGCAGACTATGC	2830	GCATAGTCTGCAGTACTGG
siRNA 1123	1123	CCTGAAGCTGACAAGTACC	2865	GGTACTTGTCAGCTTCAGG
siRNA 1127	1127	AAGCTGACAAGTACCGCCT	2869	AGGCGGTACTTGTTCAGCTT
siRNA 1128	1128	AGCTGACAAGTACCGCCTA	2870	TAGGCGGTACTTGTTCAGCT
siRNA 1130	1130	CTGACAAGTACCGCCTAAC	2872	GTTAGGCGGTACTTGTTCAG
siRNA 1134	1134	CAAGTACCGCCTAACATAT	2876	ATATGTTAGGCGGTACTTG
siRNA 1136	1136	AGTACCGCCTAACATATGC	2878	GCATATGTTAGGCGGTACT
siRNA 1137	1137	GTACCGCCTAACATATGCC	2879	GGCATATGTTAGGCGGTAC
siRNA 1138	1138	TACCGCCTAACATATGCCT	2880	AGGCATATGTTAGGCGGTAC
siRNA 1147	1147	ACATATGCCTACTTCGCTG	2889	CAGCGAAGTAGGCATATGT
siRNA 1148	1148	CATATGCCTACTTCGCTGG	2890	CCAGCGAAGTAGGCATATG
siRNA 1174	1174	GCTGGAGATGCCTTTGATG	2916	CATCAAAGGCATCTCCAGC
siRNA 1178	1178	GAGATGCCTTTGATGGCTT	2920	AAGCCATCAAAGGCATCTC
siRNA 1182	1182	TGCCTTIGATGGCTTTGAT	2924	ATCAAAGCCATCAAAGGCA
siRNA 1197	1197	TGATTTTGGCGATGATCCT	2939	AGGATCATCGCCAAAATCA
siRNA 1205	1205	GCGATGATCCTAGTGACAA	2947	TTGTCACTAGGATCATCGC
siRNA 1215	1215	TAGTGACAAGTTTTTACACA	2957	TGTGAAAACTTGTCTACTA
siRNA 1236	1236	CCATAATGGCATGCAGTTC	2978	GAACTGCATGCCATTATGG
siRNA 1243	1243	GGCATGCAGTTCAGTACCT	2985	AGGTACTGAACTGCATGCC
siRNA 1265	1265	ACAATGACAATGATAAGTT	3007	AACTTATCATTGTCTATTGT
siRNA 1278	1278	TAAGTTTGAAGGCAACTGT	3020	ACAGTTGCCTTCAAACCTTA
siRNA 1286	1286	AAGGCAACTGTGCTGAACA	3028	TGTTTCAGCACAGTTGCCTT
siRNA 1311	1311	ATCTGGTTGGTGGATGAAC	3053	GTTTCATCCACCAACCAGAT
siRNA 1315	1315	GGTTGGTGGATGAACAAGT	3057	ACTTGTTCATCCACCAACC
siRNA 1323	1323	GATGAACAAGTGTACGCT	3065	AGCGTGACACTTGTTCATC
siRNA 1324	1324	ATGAACAAGTGTACGCTG	3066	CAGCGTGACACTTGTTCAT
siRNA 1325	1325	TGAACAAGTGTACGCTGG	3067	CCAGCGTGACACTTGTTCAT
siRNA 1342	1342	GGCCATCTCAATGGAGTTT	3084	AAACTCCATTGAGATGGCC
siRNA 1344	1344	CCATCTCAATGGAGTTTAT	3086	ATAAACTCCATTGAGATGG
siRNA 1348	1348	CTCAATGGAGTTTATTACC	3090	GGTAATAAACTCCATTGAG
siRNA 1349	1349	TCAATGGAGTTTATTACCA	3091	TGGTAATAAACTCCATTGA

siRNA 1356	1356	AGTTTATTACCAAGGTGGC	3098	GCCACCTTGGTAATAAACT
siRNA 1362	1362	TTACCAAGGTGGCACTTAC	3104	GTAAGTGCCACCTTGGTAA
siRNA 1384	1384	AAAGCATCTACTCCTAATG	3126	CATTAGGAGTAGATGCTTT
siRNA 1385	1385	AAGCATCTACTCCTAATGG	3127	CCATTAGGAGTAGATGCTT
siRNA 1389	1389	ATCTACTCCTAATGGTTAT	3131	ATAACCATTAGGAGTAGAT
siRNA 1390	1390	TCTACTCCTAATGGTTATG	3132	CATAACCATTAGGAGTAGA
siRNA 1391	1391	CTACTCCTAATGGTTATGA	3133	TCATAACCATTAGGAGTAG
siRNA 1394	1394	CTCCTAATGGTTATGATAA	3136	TTATCATAACCATTAGGAG
siRNA 1396	1396	CCTAATGGTTATGATAATG	3138	CATTATCATAACCATTAGG
siRNA 1401	1401	TGGTTATGATAATGGCATT	3143	AATGCCATTATCATAACCA
siRNA 1404	1404	TTATGATAATGGCATTATT	3146	AATAATGCCATTATCATAA
siRNA 1418	1418	TTATTTGGGCCACTTGGA	3160	TTCCAAGTGGCCCAAATAA
siRNA 1420	1420	ATTTGGGCCACTTGGA	3162	TTTTCCAAGTGGCCCAAAT
siRNA 1426	1426	GCCACTTGGA	3168	ACCGGGTTTCCAAGTGGC
siRNA 1462	1462	ACCACTATGAAGATAATCC	3204	GGATTATCTTCATAGTGGT
siRNA 1482	1482	ATTCAACAGACTCACAATT	3224	AATTGTGAGTCTGTTGAAT
siRNA 1485	1485	CAACAGACTCACAATTGGA	3227	TCCAATTGTGAGTCTGTTG
siRNA 1533	1533	CAAACAGGCTGGAGACGTT	3275	AACGCTCCAGCCTGTTTG
siRNA 1540	1540	GCTGGAGACGTTTAAAAGA	3282	TCTTTTAAACGCTCCAGC
siRNA 1588	1588	GGACTTTATCTGAACAGAG	3330	CTCTGTTCAGATAAAGTCC
siRNA 1617	1617	TTTTCTTATTGGACAATG	3359	CATTGTCCAATAGGAAAAA
siRNA 1622	1622	CCTATTGGACAATGGACTT	3364	AAGTCCATTGTCCAATAGG
siRNA 1623	1623	CTATTGGACAATGGACTTG	3365	CAAGTCCATTGTCCAATAG
siRNA 1627	1627	TGGACAATGGACTTGCAA	3369	TTGCAAGTCCATTGTCCA
siRNA 1647	1647	CTTCACTTCATTTAAGAG	3389	CTCTTAAATGAAGTGAAG
siRNA 1648	1648	TTCATTCATTTAAGAGC	3390	GCTCTTAAATGAAGTGAA
siRNA 1649	1649	TCACTTCATTTAAGAGCA	3391	TGCTCTTAAATGAAGTGA
siRNA 1672	1672	ACCCCATGTTGAAA	3414	GGAGTTTTCAACATGGGGT
siRNA 1678	1678	TGTTGAAA	3420	TGTTATGGAGTTTTCAACA
siRNA 1680	1680	TTGAAA	3422	ACTGTTATGGAGTTTTCAA
siRNA 1696	1696	AGTTTATGCTGATGATAA	3438	TTATCATCAGCATAAACT
siRNA 1700	1700	TTATGCTGATGATAATTTA	3442	TAAATTATCATCAGCATAA
siRNA 1710	1710	GATAATTTATCTACATGCA	3452	TGCATGTAGATAAATTATC

[00334] The siRNAs in subset D were selected to have the following characteristics:

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

[00335] Subset E includes 53 siRNAs. The siRNAs in subset E include siRNAs from subset A and additional siRNAs that were tested in vitro (see, e.g., **Table 7**).

Table 7. Subset E siRNAs

siRNA Name	Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 233	233	CAGACAUCAUGAGUUGGUC	1975	GACCAACUCAUGAUGUCUG
siRNA 261	261	CCGGAAUUUAAUUCUCUAC	2003	GUAGAGAAUUAAAUCCGG
siRNA 274	274	CUCUACUUCUAUGCUCUUU	2016	AAAGAGCAUAGAAGUAGAG
siRNA 342	342	CUGCAUCUUAUGAUGAAAGA	2084	UCUUUCAUCUAAGAUGCAG
siRNA 343	343	UGCAUCUUAGAUGAAAGAU	2085	AUCUUUCAUCUAAGAUGCA
siRNA 344	344	GCAUCUUAGAUGAAAGAUU	2086	AAUCUUUCAUCUAAGAUGC
siRNA 347	347	UCUUAGAUGAAAGAUUCGG	2089	CCGAAUCUUUCAUCUAAGA
siRNA 349	349	UUAGAUGAAAGAUUCGGUA	2091	UACCGAAUCUUUCAUCUAA
siRNA 350	350	UAGAUGAAAGAUUCGGUAG	2092	CUACCGAAUCUUUCAUCUA
siRNA 351	351	AGAUGAAAGAUUCGGUAGU	2093	ACUACCGAAUCUUUCAUCU
siRNA 352	352	GAUGAAAGAUUCGGUAGUU	2094	AACUACCGAAUCUUUCAUC
siRNA 354	354	UGAAAGAUUCGGUAGUUAU	2096	AUAACUACCGAAUCUUUCA
siRNA 355	355	GAAAGAUUCGGUAGUUAAU	2097	AAUAACUACCGAAUCUUUC
siRNA 359	359	GAUUCGGUAGUUAAUUGUCC	2101	GGACAAUAACUACCGAAUC
siRNA 363	363	CGGUAGUUAAUUGUCCAACU	2105	AGUUGGACAAUAACUACCG
siRNA 365	365	GUAGUUAAUUGUCCAACUAC	2107	GUAGUUGGACAAUAACUAC
siRNA 367	367	AGUUAUUGUCCAACUACCU	2109	AGGUAGUUGGACAAUAACU
siRNA 397	397	GAUUUCCUGUCUACUUAUC	2139	GAUAAGUAGACAGGAAAUC
siRNA 398	398	AUUUCCUGUCUACUUAUCA	2140	UGAUAAGUAGACAGGAAAU
siRNA 423	423	AGUAGACAAGGAUCUACAG	2165	CUGUAGAUCUUGUCUACU
siRNA 432	432	GGAUCUACAGUCUUUGGAA	2174	UUCCAAAGACUGUAGAUC
siRNA 434	434	AUCUACAGUCUUUGGAAGA	2176	UCUCCAAAGACUGUAGAU
siRNA 447	447	GGAAGACAUCUUAACAUCAA	2189	UUGAUGUAAGAUGUCUCC
siRNA 449	449	AAGACAUCUUAACAUCAGU	2191	ACUUGAUGUAAGAUGUCUU
siRNA 493	493	CAGCUGAUAAAAGCAAUCC	2235	GGAUUGCUUUUAUCAGCUG
siRNA 497	497	UGAUAAAAGCAAUCCAACU	2239	AGUUGGAUUGCUUUUAUCA
siRNA 523	523	AAUCCUGAUGAAUCAUCA	2265	UUGAUGAUUCAUCAGGAU
siRNA 528	528	UGAUGAAUCAUAAAACCA	2270	UGGUUUUGAUGAUUCAUCA
siRNA 573	573	GUCCAGGAAAUGUUAGAA	2315	UUCUAACAUUUUCUGGAC
siRNA 753	753	CCAUGAUACACUGGGAAA	2495	UUUCCAGUGAUUCAUGG
siRNA 770	770	AAGAUUGUCAAGACAUUGC	2512	GCAAUGUCUUGACAAUCUU
siRNA 806	806	AGAGCGGGCUUUACUUUAU	2548	AUAAAGUAAAGCCGCUCU
siRNA 825	825	UAAACCUCUGAAAGCUAAC	2567	GUUAGCUUUCAGAGGUUUA
siRNA 929	929	UCAAGAAAAACUGGAUUCA	2671	UGAAUCCAGUUUUUCUUGA
siRNA 932	932	AGAAAAACUGGAUUCAAUA	2674	UAUUGAAUCCAGUUUUUCU
siRNA 1003	1003	GGAAAUUGAGAAGAUUCAU	2745	AAUGAAUCUUCUCAUUUCC
siRNA 1011	1011	GAAGAUUCAUUUGAUAAAGC	2753	GCUUAUCAAAUGAAUCUUC
siRNA 1013	1013	AGAUUCAUUUGAUAAAGCAC	2755	GUGCUUAUCAAAUGAAUCU
siRNA 1052	1052	CAUUAAGAGUGGAACUGGA	2794	UCCAGUCCACUCUUAUUG
siRNA 1265	1265	ACAAUGACAAUGAUAAAGUU	3007	AACUUAUCAUUGUCAUUGU
siRNA 1278	1278	UAAGUUUGAAGGCAACUGU	3020	ACAGUUGCCUCAAACUUA
siRNA 1348	1348	CUCAAUGGAGUUUAUUACC	3090	GGUAAUAAACUCCAUUGAG
siRNA 1349	1349	UCAAUUGGAGUUUAUUACCA	3091	UGGUAAUAAACUCCAUUGA

siRNA 1356	1356	AGUUUAUUACCAAGGUGGC	3098	GCCACCUUGGUAAAUAACU
siRNA 1384	1384	AAAGCAUCUACUCCUAAUG	3126	CAUUAGGAGUAGAUGCUIU
siRNA 1385	1385	AAGCAUCUACUCCUAAUGG	3127	CCAUUAGGAGUAGAUGCUIU
siRNA 1389	1389	AUCUACUCCUAAUGGUUAU	3131	AUAACCAUUAGGAGUAGAU
siRNA 1390	1390	UCUACUCCUAAUGGUUAUG	3132	CAUAACCAUUAGGAGUAGA
siRNA 1391	1391	CUACUCCUAAUGGUUAUGA	3133	UCAUAACCAUUAGGAGUAG
siRNA 1394	1394	CUCCUAAUGGUUAUGAUAA	3136	UUAUCAUAACCAUUAGGAG
siRNA 1396	1396	CCUAAUGGUUAUGAUAAUG	3138	CAUUAUCAUAACCAUUAGG
siRNA 1418	1418	UUAUUUGGGCCACUUGGAA	3160	UCCAAGUGGCCCAAAUAA
siRNA 1462	1462	ACCACUAUGAAGAUAAUCC	3204	GGAUUAUCUUAUAGUGGU

[00336] In some cases, the sense strand of any of the siRNAs of subset E comprises siRNA with a particular modification pattern. In this example modification pattern, position 9 counting from the 5' end of the of the sense strand is has the 2'F modification. Where a "2'F modification" is denoted, it is intended to mean that a 2'F is included. In this example modification pattern, when position 9 of the sense strand is a pyrimidine, then all purines in the sense strand have the 2'Ome modification. Where a "2'Ome modification" is denoted, it is intended to mean that a 2'Ome is included. In this example modification pattern, when position 9 is the only pyrimidine between positions 5 and 11 of the sense stand, then position 9 is the only position with the 2'F modification in the sense strand. In this example modification pattern, when position 9 and only one other base between positions 5 and 11 of the sense strand are pyrimidines, then both of these pyrimidines are the only two positions with the 2'F modification in the sense strand. In this example modification pattern, when position 9 and only two other bases between positions 5 and 11 of the sense strand are pyrimidines, and those two other pyrimidines 're in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In this example modification pattern, when there are >2 pyrimidines between positions 5 and 11 of the sense strand, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row.

[00337] In this example modification pattern, when position 9 of the sense strand is a purine, then all purines in the sense strand have the 2'Ome modification. In this example modification pattern, when position 9 is the only purine between positions 5 and 11 of the sense stand, then position 9 is the only position with the 2'F modification in the sense strand. In this example modification pattern, when position 9 and only one other base between positions 5 and 11 of the sense strand are purines, then both of these purines are the only two positions with the 2'F modification in the sense strand. In this example modification pattern, when position 9 and only two other bases between positions 5 and 11 of the sense strand are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In this example modification pattern, when there are >2 purines between positions 5 and 11 of the sense strand, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F

modifications in a row. In some cases, the sense strand of any of the siRNAs of subset E comprises a modification pattern which conforms to these sense strand rules (Table 8A).

[00338] In some cases, the antisense strand of any of the siRNAs of subset E comprises modification pattern 9AS (Table 8A). The siRNAs in subset E may comprise any other modification pattern(s).

Table 8A. Modified siRNA sequences

siRNA Name	Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
ETD01663	3485	cagacAfucAfuGfaguugguasusu	3538	uAfcCfaAfcUfcAfuGfaUfgUfcUfgsusu
ETD01664	3486	ccggaaUfuUfaauucucuaasusu	3539	uUfaGfaGfaAfuUfaAfaUfuCfcGfgsusu
ETD01665	3487	cucuaCfuUfUfCfuFaugcucuuasusu	3540	uAfaGfaGfcAfuAfgAfaGfuAfgAfgsusu
ETD01666	3488	cugcaUfCfuUfUfagaagaasusu	3541	uCfuUfuCfaUfcUfaAfgAfuGfcAfgsusu
ETD01667	3489	ugcaucuuAfGfauaagaasusu	3542	uUfcUfuUfcAfuCfuAfaGfaUfgCfasusu
ETD01668	3490	gcaucuuAfGfauaagaasusu	3543	uAfuCfuUfuCfaUfcUfaAfgAfuGfcsusu
ETD01669	3491	ucuuAfGfauGfaAfauguasusu	3544	uCfcAfaUfcUfuUfcAfuCfuAfaGfasusu
ETD01670	3492	uuagAfuGfAfaAfauguasusu	3545	uAfcCfcAfaUfcUfuUfcAfuCfuAfasusu
ETD01671	3493	uagauGfAfaAfaAfuucguasusu	3546	uUfaCfcGfaAfuCfuUfuCfaUfcUfasusu
ETD01672	3494	agauGfAfaAfaGfauucguasusu	3547	uCfuAfcCfcAfaUfcUfuUfcAfuCfususu
ETD01673	3495	gaugAfaAfaGfAfuucguasusu	3548	uAfcUfaCfcGfaAfuCfuUfuCfaUfcusu
ETD01674	3496	ugaagaUfUfcguaguuaasusu	3549	uUfaAfcUfaCfcGfaAfuCfuUfuCfasusu
ETD01675	3497	gaaagaUfUfcguaguuaasusu	3550	uAfuAfaCfuAfcCfcAfaUfcUfuUfcusu
ETD01676	3498	gauucGfGfuAfGfuuaugucasusu	3551	uGfaCfaAfuAfaCfuAfcCfcAfaUfcusu
ETD01677	3499	cggUfGfuUfUfuguccaacasusu	3552	uGfuUfgGfaCfaAfuAfaCfuAfcCfcusu
ETD01678	3500	guagUfUfaUfUfgUfccacaasusu	3553	uUfaGfuUfgGfaCfaAfuAfaCfuAfcusu
ETD01679	3501	aguuaUfUfgUfcCfaacuacasusu	3554	uGfgUfaGfuUfgGfaCfaAfuAfaCfususu
ETD01680	3502	gauuuccUfGfucacuuaasusu	3555	uAfuAfaGfuAfgAfcAfgGfaAfaUfcusu
ETD01681	3503	auuuCfCfuUfUfacuuaacasusu	3556	uGfaUfaAfgUfaGfaCfaGfgAfaUfcusu
ETD01682	3504	aguaGfAfaAfaGfaucaacasusu	3557	uUfgUfaGfaUfcCfuUfgUfcUfaCfususu
ETD01683	3505	ggauCuAfcAfGfucuuuggaasusu	3558	uUfcCfaAfaGfaCfuGfuAfgAfuCfcusu
ETD01684	3506	aucuaCfagUfcUfuuggaasusu	3559	uCfuUfcCfaAfaGfaCfuGfuAfgAfususu
ETD01685	3507	ggaagaCfaUfcUfacaacaasusu	3560	uUfgAfuGfuAfaGfaUfgUfcUfuCfcusu
ETD01686	3508	aagaCfaUfCfuUfUfacaacaasusu	3561	uCfuUfgAfuGfuAfaGfaUfgUfcUfususu
ETD01687	3509	cagcuGfAfuAfaAfaagcaacasusu	3562	uGfaUfuGfcUfuUfuAfuCfaGfcUfgsusu
ETD01688	3510	ugauAfaAfaAfaAfaucacaacasusu	3563	uGfuUfgGfaUfuGfcUfuUfuAfuCfasusu
ETD01689	3511	aaucCfUfgaUfgaaucaacasusu	3564	uUfgAfuGfaUfuCfaUfcAfgGfaUfususu
ETD01690	3512	ugaugaaUfCfaUfcaaaacasusu	3565	uGfgUfuUfuGfaUfgAfuUfcAfuCfasusu
ETD01691	3513	guccAfGfgAfAfaAfuuuagaasusu	3566	uUfcUfaAfcAfuUfuUfcCfuGfgAfcusu
ETD01692	3514	ccaugaUfaUfCfucgggaasusu	3567	uUfuCfcCfaGfuGfaUfaUfcAfuGfgsusu
ETD01693	3515	aagaUfUfgUfCfaagacauugasusu	3568	uCfaAfuGfuCfuUfgAfcAfaUfcUfususu
ETD01694	3516	agagCfaggCfuUfuacuuuacasusu	3569	uUfaAfaGfuAfaAfgCfcCfcCfuCfususu
ETD01695	3517	uaaaCfCfuUfCfuUfgaaagcuacasusu	3570	uUfuAfgCfuUfuCfaGfaGfgUfuUfasusu
ETD01696	3518	ucaaGfAfaAfaAfaacuggaucasusu	3571	uGfaAfuCfcAfgUfuUfuUfcUfuGfasusu
ETD01697	3519	agaaaaCfUfggaucuuasusu	3572	uAfuUfgAfaUfcCfaGfuUfuUfuCfususu
ETD01698	3520	ggaaAfuGfAfaAfaagaucauasusu	3573	uAfuGfaAfuCfuUfcUfcAfuUfuCfcusu
ETD01699	3521	gaagAfuucAfuugauaagasusu	3574	uCfuUfaUfcAfaAfuGfaAfuCfuUfcusu
ETD01700	3522	agauUfCfaUfUfugaauagcaasusu	3575	uUfgCfuUfaUfcAfaAfuGfaAfuCfususu
ETD01701	3523	cauuAfAfgAfGfuGfgaacuggasusu	3576	uCfcAfgUfuCfcAfcUfcUfuAfaUfgsusu
ETD01702	3524	acaauGfAfaAfaAfaagauasusu	3577	uAfcUfuAfuCfaUfuGfuCfaUfuGfususu
ETD01703	3525	uaaguuuGfAfaAfaGfgcaacugasusu	3578	uCfaGfuUfgCfcUfuCfaAfaCfuUfasusu
ETD01704	3526	cucaAfuGfGfAfaGfuuuuauacasusu	3579	uGfuAfaUfaAfaCfuCfcAfuUfgAfgsusu
ETD01705	3527	ucaaGfGfAfaGfuuuuauacasusu	3580	uGfgUfaAfuAfaAfcUfcCfaUfuGfasusu

ETD01706	3528	aguuuAfuuAfccaagguggasusu	3581	uCfcAfcCfuUfgGfuAfaUfaAfaCfususu
ETD01707	3529	aaagCfaUfcUfaCfuccuaauasusu	3582	uAfuUfaGfgAfgUfaGfaUfgCfuUfususu
ETD01708	3530	aagcAfucuAfcuccuaaugasusu	3583	uCfaUfuAfgGfaGfuAfgAfuGfcUfususu
ETD01709	3531	aucuaCfUfCfCfUfaaugguuauasusu	3584	uUfaAfcCfaUfuAfgGfaGfuAfgAfususu
ETD01710	3532	ucuaCfUfCfCfUfaaugguuauasusu	3585	uAfuAfaCfcAfuUfaGfgAfgUfaGfasusu
ETD01711	3533	cuacuccuAfAfuGfgguuauasusu	3586	uCfaUfaAfcCfaUfuAfgGfaGfuAfgsusu
ETD01712	3534	cuccuAfAfuGfGfuuaugauaasusu	3587	uUfaUfcAfuAfaCfcAfuUfaGfgAfgsusu
ETD01713	3535	ccuaaUfggUfUfaugauaauasusu	3588	uAfuUfaUfcAfuAfaCfcAfuUfaGfgsusu
ETD01714	3536	uuauuuGfgGfccacuuggaasusu	3589	uUfcCfaAfgUfgGfcCfcAfaAfuAfasusu
ETD01715	3537	accacuAfuGfaAfgauaauacasusu	3590	uGfaUfuAfuCfuUfcAfuAfgUfgGfususu

[00339] In Table 8A, Nf (Af, Cf, Gf, Uf, or Tf) is a 2' fluoro-modified nucleoside, n (a, c, g, u, or t) is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00340] Any siRNA among any of subsets A-E may comprise any modification pattern described herein. If a sequence is a different number of nucleotides in length than a modification pattern, the modification pattern may still be used with the appropriate number of additional nucleotides added 5' or 3' to match the number of nucleotides in the modification pattern. For example, if a sense or antisense strand of the siRNA among any of subsets A-E comprises 19 nucleotides, and a modification pattern comprises 21 nucleotides, UU may be added onto the 5' end of the sense or antisense strand.

Using a different algorithm for analyzing siRNA specificity, an additional bioinformatically selected set of siRNAs was generated. Prioritizing sequences for target specificity, species cross-reactivity, miRNA seed region sequences and SNPs as described above yields subset G. Subset G contains 131 siRNAs whose base sequences are shown in Table 8B.

Table 8B: Subset G siRNAs

Sense strand SEQ ID NO:	Sense strand sequence (5'-3')	Antisense strand SEQ ID NO:	Antisense strand sequence (5'-3')
236	ACATCATGAGTTGGTCCTT	1978	AAGGACCAACTCATGATGT
243	GAGTTGGTCCTTGACCCC	1985	GGGGTGCAAGGACCAACTC
259	CCCCGGAATTTAATTCTCT	2001	AGAGAATTAAATTCCGGGG
264	GAATTTAATTCTCTACTTC	2006	GAAGTAGAGAATTAAATTC
276	CTACTTCTATGCTCTTTTA	2018	TAAAAGAGCATAGAAGTAG
305	CAACATGTGTAGCATATGT	2047	ACATATGCTACACATGTIG
307	ACATGTGTAGCATATGTIG	2049	CAACATATGCTACACATGT
312	TGTAGCATATGTTGCTACC	2054	GGTAGCAACATATGCTACA
321	TGTTGCTACCAGAGACAAC	2063	GTTGTCTCTGGTAGCAACA
325	GCTACCAGAGACAACCTGCT	2067	AGCAGTTGTCTCTGGTAGC
326	CTACCAGAGACAACCTGCTG	2068	CAGCAGTTGTCTCTGGTAG
330	CAGAGACAACCTGCTGCATC	2072	GATGCAGCAGTTGTCTCTG
346	ATCTTAGATGAAAGATTCTG	2088	CGAATCTTTCATCTAAGAT
357	AAGATTCCGGTAGTTATTGT	2099	ACAATAACTACCGAATCTT
370	TATTGTCCAACCTACCTGTG	2112	CACAGGTAGTTGGACAATA
371	ATTGTCCAACCTACCTGTGG	2113	CCACAGGTAGTTGGACAAT
374	GTCCAACCTACCTGTGGCAT	2116	ATGCCACAGGTAGTTGGAC
375	TCCAACCTACCTGTGGCATT	2117	AATGCCACAGGTAGTTGGA
385	TGTGGCATTGCAGATTTC	2127	GGAAATCTGCAATGCCACA

393	TGCAGATTTCTGTCTACT	2135	AGTAGACAGGAAATCTGCA
408	TACTTATCAAACCAAAGTA	2150	TACTTTGGTTTGATAAGTA
413	ATCAAACCAAAGTAGACAA	2155	TTGTCTACTTTGGTTTGAT
425	TAGACAAGGATCTACAGTC	2167	GA CTGTAGATCCTTGTCTA
443	CTTTGGAAGACATCTTACA	2185	TGTAAGATGTCTTCCAAAG
451	GACATCTTACATCAAGTTG	2193	CAACTTGATGTAAGATGTC
496	CTGATAAAAGCAATCCAAC	2238	GTTGGATTGCTTTTATCAG
498	GATAAAAGCAATCCAACTC	2240	GAGTTGGATTGCTTTTATC
503	AAGCAATCCAAC TACTTA	2245	TAAGTGAGTTGGATTGCTT
506	CAATCCAAC TCACTTATAA	2248	TTATAAGTGAGTTGGATTG
545	CAAATATGATAGACGCTGC	2287	GCAGCGTCTATCATATTTG
553	ATAGACGCTGCTACTTTGA	2295	TCAAAGTAGCAGCGTCTAT
560	CTGCTACTTTGAAGTCCAG	2302	CTGGACTTCAAAGTAGCAG
565	ACTTTGAAGTCCAGGAAAA	2307	TTTTCTGGACTTCAAAGT
602	AATATGAAGCATCGATTTT	2344	AAAATCGATGCTTCATATT
603	ATATGAAGCATCGATTTTA	2345	TAAAATCGATGCTTCATAT
626	ATGACTCAAGTATTCGATA	2368	TATCGAATACTTGAGTCAT
670	AATCAAAAGATTGTTAACCC	2412	GGTTAAACAATCTTTTGATT
674	AAAAGATTGTTAACCTGAA	2416	TTCAGGTTAAACAATCTTTT
694	GAGAAGGTAGCCAGCTTG	2436	CAAGCTGGGCTACCTTCTC
726	GGAACCTTGCAAAGACACG	2468	CGTGTCTTTGCAAAGTTCC
742	ACGGTGCAAATCCATGATA	2484	TATCATGGATTTCACCCGT
743	CGGTGCAAATCCATGATAT	2485	ATATCATGGATTTCACCCG
747	GCAAATCCATGATATCACT	2489	AGTGATATCATGGATTTCG
755	ATGATATCACTGGGAAAGA	2497	TCTTTCCAGTGATATCAT
776	GTCAAGACATTGCCAATAA	2518	TTATTGGCAATGCTTGAC
779	AAGACATTGCCAATAAGGG	2521	CCCTTATTGGCAATGCTT
789	CAATAAGGGAGCTAAACAG	2531	CTGTTTAGCTCCCTTATTG
793	AAGGGAGCTAAACAGAGCG	2535	CGCTCTGTTTAGCTCCCTT
799	GCTAAACAGAGCGGGCTTT	2541	AAAGCCCCGCTCTGTTTAGC
803	AACAGAGCGGGCTTTACTT	2545	AAGTAAAGCCCCGCTCTGTT
836	AAGCTAACCAGCAATTCTT	2578	AAGAATTGCTGGTTAGCTT
856	GTCTACTGTGAAATCGATG	2598	CATCGATTTACAGTAGAC
867	AATCGATGGGTCTGGAAAT	2609	ATTTCCAGACCCATCGATT
875	GGTCTGGAAATGGATGGAC	2617	GTCCATCCATTTCCAGACC
876	GTCTGGAAATGGATGGACT	2618	AGTCCATCCATTTCCAGAC
950	ATAAAGAAGGATTTGGACA	2692	TGTCCAAATCCTTCTTTAT
970	CTGTCTCCTACTGGCACA	2712	TTGTGCCAGTAGGAGACAG
971	TGTCTCCTACTGGCACAAC	2713	GTTGTGCCAGTAGGAGACA
985	ACAACAGAATTTGGCTGG	2727	CCAGCCAAAATTCGTGTTGT
1000	CTGGGAAATGAGAAGATTC	2742	GAATCTTCTCATTTCCAG
1008	TGAGAAGATTCATTTGATA	2750	TATCAAATGAATCTTCTCA
1009	GAGAAGATTCATTTGATAA	2751	TTATCAAATGAATCTTCTC
1020	TTTGATAAGCACACAGTCT	2762	AGACTGTGTGCTTATCAAA
1023	GATAAGCACACAGTCTGCC	2765	GGCAGACTGTGTGCTTATC
1033	CAGTCTGCCATCCCATATG	2775	CATATGGGATGGCAGACTG
1037	CTGCCATCCCATATGCATT	2779	AATGCATATGGGATGGCAG
1038	TGCCATCCCATATGCATTA	2780	TAATGCATATGGGATGGCA

1044	CCCATATGCATTAAGAGTG	2786	CACTCTTAATGCATATGGG
1045	CCATATGCATTAAGAGTG	2787	CCACTCTTAATGCATATGG
1081	GGCAGAACCAGTACTGCAG	2823	CTGCAGTACTGGTTCTGCC
1090	AGTACTGCAGACTATGCCA	2832	TGGCATAGTCTGCAGTACT
1099	GA CTATGCCATGTTCAAGG	2841	CCTTGAACATGGCATAGTC
1100	ACTATGCCATGTTCAAGGT	2842	ACCTTGAACATGGCATAGT
1114	AAGGTGGGACCTGAAGCTG	2856	CAGCTTCAGGTCCCACCTT
1152	TGCCTACTTCGCTGGTGGG	2894	CCCACCAGCGAAGTAGGCA
1156	TACTTCGCTGGTGGGGATG	2898	CATCCCCACCAGCGAAGTA
1196	TTGATTTTGCGGATGATCC	2938	GGATCATCGCCAAAATCAA
1199	ATTTTGCGGATGATCCTAG	2941	CTAGGATCATCGCCAAAAT
1211	ATCCTAGTGACAAGTTTTT	2953	AAAAAACTTGTCACTAGGAT
1212	TCCTAGTGACAAGTTTTTC	2954	GAAAAAACTTGTCACTAGGA
1213	CCTAGTGACAAGTTTTTCA	2955	TGAAAAAACTTGTCACTAGG
1218	TGACAAGTTTTTTCACATCC	2960	GGATGTGAAAAAACTTGTC
1219	GACAAGTTTTTTCACATCCC	2961	GGGATGTGAAAAAACTTGTC
1231	ACATCCCATAATGGCATGC	2973	GCATGCCATTATGGGATGT
1232	CATCCCATAATGGCATGCA	2974	TGCATGCCATTATGGGATG
1241	ATGGCATGCAGTTCAGTAC	2983	GTA CTGAACTGCATGCCAT
1245	CATGCAGTTCAGTACCTGG	2987	CCAGGTACTGAACTGCATG
1250	AGTTCAGTACCTGGGACAA	2992	TTGTCCCAGGTACTGAACT
1252	TTCAGTACCTGGGACAATG	2994	CATTGTCCCAGGTACTGAA
1269	TGACAATGATAAGTTTGAA	3011	TTCAAACCTATCATTTGTCA
1273	AATGATAAGTTTGAAGGCA	3015	TGCCTTCAAACCTATCATT
1279	AAGTTTGAAGGCAACTGTG	3021	CACAGTTGCCTTCAAACCTT
1303	CAGGATGGATCTGGTTGGT	3045	ACCAACCAGATCCATCCTG
1305	GGATGGATCTGGTTGGTGG	3047	CCACCAACCAGATCCATCC
1327	AACAAGTGTCACGCTGGCC	3069	GGCCAGCGTGACACTTGTT
1329	CAAGTGTCACGCTGGCCAT	3071	ATGGCCAGCGTGACACTTG
1334	GTCACGCTGGCCATCTCAA	3076	TTGAGATGGCCAGCGTGAC
1355	GAGTTTATTACCAAGGTGG	3097	CCACCTTGGTAATAAACTC
1357	GTTTATTACCAAGGTGGCA	3099	TGCCACCTTGGTAATAAAC
1363	TACCAAGGTGGCACTTACT	3105	AGTAAGTGCCACCTTGGTA
1364	ACCAAGGTGGCACTTACTC	3106	GAGTAAGTGCCACCTTGGT
1367	AAGGTGGCACTTACTCAAA	3109	TTTGAGTAAGTGCCACCTT
1371	TGGCACTTACTCAAAAGCA	3113	TGCTTTTGAGTAAGTGCCA
1388	CATCTACTCCTAATGGTTA	3130	TAACCATTAGGAGTAGATG
1392	TACTCCTAATGGTTATGAT	3134	ATCATAACCATTAGGAGTA
1424	GGGCCACTTGGA AAAACCCG	3166	CGGGTTTTCCAAGTGGCCC
1429	ACTTGGA AAAACCCGGTGGT	3171	ACCACCGGGTTTTCCAAGT
1430	CTTGGA AAAACCCGGTGGTA	3172	TACCACCGGGTTTTCCAAG
1433	GGAAAACCCGGTGGTATTC	3175	GAATAACCACCGGGTTTTCC
1471	AAGATAATCCCATTC AACA	3213	TGTTGAATGGGATTATCTT
1472	AGATAATCCCATTC AACAG	3214	CTGTTGAATGGGATTATCT
1476	AATCCCATTC AACAGACTC	3218	GAGTCTGTTGAATGGGATT
1486	AACAGACTCACAATTGGAG	3228	CTCCAATTGTGAGTCTGTT
1489	AGACTCACAATTGGAGAAG	3231	CTTCTCCAATTGTGAGTCT
1516	CACCACCTGGGGGGAGCCA	3258	TGGCTCCCCCAGGTGGTG

1518	CCACCTGGGGGGAGCCAAA	3260	TTTGGCTCCCCCAGGTGG
1524	GGGGGAGCCAAACAGGCT	3266	AGCCTGTTTGGCTCCCCC
1525	GGGGGAGCCAAACAGGCTG	3267	CAGCCTGTTTGGCTCCCCC
1526	GGGGAGCCAAACAGGCTGG	3268	CCAGCCTGTTTGGCTCCCC
1534	AAACAGGCTGGAGACGTTT	3276	AAACGTCTCCAGCCTGTTT
1539	GGCTGGAGACGTTTAAAG	3281	CTTTTAAACGTCTCCAGCC
1593	TTATCTGAACAGAGAGATA	3335	TATCTCTCTGTTTCAGATA
1594	TATCTGAACAGAGAGATAT	3336	ATATCTCTCTGTTTCAGATA
1598	TGAACAGAGAGATATAATA	3340	TATTATATCTCTCTGTTCA
1600	AACAGAGAGATATAATATT	3342	AATATTATATCTCTCTGTT
1601	ACAGAGAGATATAATATTT	3343	AAATATTATATCTCTCTGTT
1614	ATATTTTTCCTATTGGACA	3356	TGTCCAATAGGAAAAATAT
1616	ATTTTTCCTATTGGACAAT	3358	ATTGTCCAATAGGAAAAAT
1650	CACTTCATTTTAAGAGCAA	3392	TTGCTCTTAAAATGAAGTG
1693	AACAGTTTTATGCTGATGA	3435	TCATCAGCATAAACTGTT
1703	TGCTGATGATAATTTATCT	3445	AGATAAATTATCATCAGCA
1044	CCCATATGCATTAAGAGTG	2786	CACTCTTAATGCATATGGG
1045	CCATATGCATTAAGAGTGG	2787	CCACTCTTAATGCATATGG
1081	GGCAGAACCAGTACTGCAG	2823	CTGCAGTACTGGTTCCTGCC
1090	AGTACTGCAGACTATGCCA	2832	TGGCATAGTCTGCAGTACT
1099	GACTATGCCATGTTCAAGG	2841	CCTTGAACATGGCATAGTC
1100	ACTATGCCATGTTCAAGGT	2842	ACCTTGAACATGGCATAGT
1114	AAGGTGGGACCTGAAGCTG	2856	CAGCTTCAGGTCCCACCTT
1152	TGCCTACTTCGCTGGTGGG	2894	CCCACCAGCGAAGTAGGCA
1156	TACTTCGCTGGTGGGGATG	2898	CATCCCCACCAGCGAAGTA
1196	TTGATTTTGGCGATGATCC	2938	GGATCATCGCCAAAATCAA
1199	ATTTTGGCGATGATCCTAG	2941	CTAGGATCATCGCCAAAAT
1211	ATCCTAGTGACAAGTTTTT	2953	AAAAAATTGTCACTAGGAT
1212	TCCTAGTGACAAGTTTTTC	2954	GAAAAAATTGTCACTAGGA
1213	CCTAGTGACAAGTTTTTCA	2955	TGAAAAAATTGTCACTAGG
1218	TGACAAGTTTTTCACATCC	2960	GGATGTGAAAAAATTGTCA
1219	GACAAGTTTTTCACATCCC	2961	GGGATGTGAAAAAATTGTCA
1231	ACATCCCATAATGGCATGC	2973	GCATGCCATTATGGGATGT
1232	CATCCCATAATGGCATGCA	2974	TGCATGCCATTATGGGATG
1241	ATGGCATGCAGTTCAGTAC	2983	GTAAGTGAAGTGCATGCCAT
1245	CATGCAGTTCAGTACCTGG	2987	CCAGGTACTGAACTGCATG
1250	AGTTCAGTACCTGGGACAA	2992	TTGTCCCAGGTACTGAACT
1252	TTCAGTACCTGGGACAATG	2994	CATTGTCCCAGGTACTGAA
1269	TGACAATGATAAGTTTGAA	3011	TTCAAACCTTATCATTGTCA
1273	AATGATAAGTTTGAAGGCA	3015	TGCCTTCAAACCTTATCATT
1279	AAGTTTGAAGGCAACTGTG	3021	CACAGTTGCCTTCAAACCTT
1303	CAGGATGGATCTGGTTGGT	3045	ACCAACCAGATCCATCCTG
1305	GGATGGATCTGGTTGGTGG	3047	CCACCAACCAGATCCATCC
1327	AACAAGTGTACGCTGGCC	3069	GGCCAGCGTGACACTTGTT
1329	CAAGTGTACGCTGGCCAT	3071	ATGGCCAGCGTGACACTTG
1334	GTCACGCTGGCCATCTCAA	3076	TTGAGATGGCCAGCGTGAC
1355	GAGTTTATTACCAAGGTGG	3097	CCACCTTGGTAATAAACTC
1357	GTTTATTACCAAGGTGGCA	3099	TGCCACCTTGGTAATAAAC

1363	TACCAAGGTGGCACTTACT	3105	AGTAAGTGCCACCTTGGTA
1364	ACCAAGGTGGCACTTACTC	3106	GAGTAAGTGCCACCTTGGT
1367	AAGGTGGCACTTACTCAAA	3109	TTTGAGTAAGTGCCACCTT
1371	TGGCACTTACTCAAAAGCA	3113	TGCTTTTGAGTAAGTGCCA
1388	CATCTACTCCTAATGGTTA	3130	TAACCATTAGGAGTAGATG
1392	TACTCCTAATGGTTATGAT	3134	ATCATAACCATTAGGAGTA
1424	GGGCCACTTGGAACCCCG	3166	CGGGTTTTTCCAAGTGGCCC
1429	ACTTGGAACCCCGGTGGT	3171	ACCACCGGGTTTTCCAAGT
1430	CTTGGAACCCCGGTGGTA	3172	TACCACCGGGTTTTCCAAG
1433	GGAAACCCCGGTGGTATTC	3175	GAATACCACCGGGTTTTCC
1471	AAGATAATCCCATTCACAA	3213	TGTTGAATGGGATTATCTT
1472	AGATAATCCCATTCACAG	3214	CTGTTGAATGGGATTATCT
1476	AATCCCATTCACAGACTC	3218	GAGTCTGTTGAATGGGATT
1486	AACAGACTCACAATTGGAG	3228	CTCCAATTGTGAGTCTGTT
1489	AGACTCACAATTGGAGAAG	3231	CTTCTCCAATTGTGAGTCT
1516	CACCACCTGGGGGGAGCCA	3258	TGGCTCCCCCAGGTGGTG
1518	CCACCTGGGGGGAGCCAAA	3260	TTTGGCTCCCCCAGGTGG
1524	GGGGGGAGCCAAACAGGCT	3266	AGCCTGTTTGGCTCCCCC
1525	GGGGGAGCCAAACAGGCTG	3267	CAGCCTGTTTGGCTCCCCC
1526	GGGGAGCCAAACAGGCTGG	3268	CCAGCCTGTTTGGCTCCCC
1534	AAACAGGCTGGAGACGTTT	3276	AAACGTCTCCAGCCTGTTT
1539	GGCTGGAGACGTTTAAAAG	3281	CTTTTAAACGTCTCCAGCC
1593	TTATCTGAACAGAGAGATA	3335	TATCTCTCTGTTTCAGATAA
1594	TATCTGAACAGAGAGATAT	3336	ATATCTCTCTGTTTCAGATA
1598	TGAACAGAGAGATATAATA	3340	TATTATATCTCTCTGTTCA
1600	AACAGAGAGATATAATATT	3342	AATATTATATCTCTCTGTT
1601	ACAGAGAGATATAATATTT	3343	AAATATTATATCTCTCTGT
1614	ATATTTTCTTATTGGACA	3356	TGTCCAATAGGAAAAATAT
1616	ATTTTCTTATTGGACAAT	3358	ATTGTCCAATAGGAAAAAT
1650	CACTTCATTTTAAGAGCAA	3392	TTGCTCTTAAAATGAAGTG
1693	AACAGTTTTATGCTGATGA	3435	TCATCAGCATAAACTGTT
1703	TGCTGATGATAATTTATCT	3445	AGATAAATTATCATCAGCA

[00341] The siRNAs in subset G have the following characteristics:

- Cross-reactivity: With 19mer in human FGG mRNA, with 17mer/19mer in NHP FGG
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species
- Off-target frequency: ≤ 30 human off-targets matched with 2 mismatches in antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF $\geq 1\%$ (pos. 2-18)

Example 3: Screening FGG siRNAs for activity in Hep 3B2.1-7 cells in culture

[00342] Chemically modified FGG siRNAs cross reactive for at least human and non-human primates will be assayed for FGG mRNA knockdown activity in cells in culture. Hep 3B2.1-7 cells (ATCC® catalog# HB-8064) will be seeded in 96-well tissue culture plates at a cell density of 7,500 cells per well in EMEM media (VWR catalog# 76000-922) supplemented with 10% fetal bovine serum and incubated

overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere without supplemental carbon dioxide. The FGG siRNAs will be individually transfected into Hep 3B2.1-7 cells in duplicate wells at 1 nM and 10 nM final concentration using 0.3 µL Lipofectamine RNAiMax (Fisher, catalog# 13778150) in 5 uL Opti-MEM (Thermo Fisher, catalog# 31985070) per well. Silencer Select Negative Control #3 (ThermoFisher, Catalog# 4392420 ID s51788) will be transfected at 1 nM and 10 nM final concentrations as a control. A positive control siRNA (ThermoFisher, Catalog#) will be transfected at 1 nM and 10 nM final concentrations. After incubation for 48 hours at 37°C, total RNA will be harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, catalog# A35374) according to the manufacturer's instructions. The level of FGG mRNA from each well will be measured in triplicate by biplex real-time qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan Gene Expression Assay for human FGG (ThermoFisher, assay# Hs00241037_m1). The level of PPIA mRNA will be measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative FGG mRNA levels in each well using the delta-delta Ct method. All data will be normalized to relative FGG mRNA levels in untreated Hep 3B2.1-7 cells. Identification of siRNAs targeting FGG that reduce FGG expression is anticipated.

Example 4: Determining the IC50 of FGG siRNAs

[00343] The IC50 values for knockdown of FGG mRNA by select FGG siRNAs will be determined in Hep 3B2.1-7 cells. The siRNAs will be assayed individually in triplicate at 30 nM, 10 nM, 3 nM, 1 nM and 0.3 nM, 0.1 nM and 0.03 nM. Hep 3B2.1-7 cells (ATCC® catalog# HB-8064) will be seeded in 96-well tissue culture plates at a cell density of 7,500 cells per well in EMEM media (VWR catalog# 76000-922) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere without supplemental carbon dioxide. The FGG siRNAs will be individually transfected using 0.3 µL Lipofectamine RNAiMax (Fisher, catalog# 13778150) in 5 uL Opti-MEM (Thermo Fisher, catalog# 31985070) per well. After incubation for 48 hours at 37°C, total RNA will be harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of FGG mRNA from each well will be measured in triplicate by biplex real-time qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan Gene Expression Assay for human FGG (ThermoFisher, assay# Hs00241037_m1). The level of PPIA mRNA will be measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative FGG mRNA levels in each well using the delta-delta Ct method. All data will be normalized to relative FGG mRNA levels in untreated Hep 3B2.1-7 cells. Curve fit will be accomplished using the [inhibitor] vs. response (three parameters) function in GraphPad Prism software.

Example 5: ASO-mediated knockdown of FGG in HEPG2 cell line

[00344] ASOs targeted to the FGG mRNA that downregulate levels of FGG mRNA leading to a decrease in FGG secretion, when administered to the cultured human hepatocyte cell line, HepG2.

[00345] On Day 0, the HEPG2 cells are seeded at 150,000 cells/mL into a Falcon 24-well tissue culture plate (ThermoFisher Cat. No. 353047) at 0.5 mL per well.

[00346] On Day 1, the FGG ASO and negative control ASO master mixes are prepared. The FGG ASO master mix contains 350 μ L of Opti-MEM (ThermoFisher Cat. No. 4427037 – s1288 Lot No. AS02B02D) and 3.5 μ L of a FGG ASO (10 μ M stock). The negative control ASO master mix contains 350 μ L of Opti-MEM and 3.5 μ L of negative control ASO (ThermoFisher Cat. No. 4390843, 10 μ M stock). Next, 3 μ L of TransIT-X2 (Mirus Cat. No. MIR-6000) is added to each master mix. The mixes are incubated for 15 minutes to allow transfection complexes to form, then 51 μ L of the appropriate master mix + TransIT-X2 is added to duplicate wells of HEPG2 cells with a final ASO concentration of 10 nM.

[00347] On Day 3, 48 hours post transfection, media is collected and mixed with protein lysis buffer containing protease and phosphatase inhibitors, and the cells are lysed using the Cells-to-Ct kit according to the manufacturer's protocol (ThermoFisher Cat. No. 4399002). For the Cells-to-Ct, cells are washed with 50 μ L using cold 1X PBS and lysed by adding 49.5 μ L of Lysis Solution and 0.5 μ L Dnase I per well and pipetting up and down 5 times and incubating for 5 minutes at room temperature. The Stop Solution (5 μ L/well) is added to each well and mixed by pipetting up and down five times and incubating at room temperature for 2 minutes. The reverse transcriptase reaction is performed using 22.5 μ L of the lysate according to the manufacturer's protocol. Samples are stored at -80 °C until real-time qPCR is performed in triplicate using TaqMan Gene Expression Assays (Applied Biosystems FAM/FGG using a BioRad CFX96 Cat. No. 1855195). For the protein quantification, equivalent quantities (30–50 μ g) of protein are separated by 10% SDS polyacrylamide gels and transferred to polyvinylidene fluoride membranes. Membranes are blocked with 5% nonfat milk and incubated overnight with the appropriate primary antibody at dilutions specified by the manufacturer. Next, the membranes are washed three times in TBST and incubated with the corresponding horseradish peroxidase conjugated secondary antibody at 1:5,000 dilution for 1 hr. Bound secondary antibody is detected using an enhanced chemiluminescence system. The primary immunoblotting antibody is an anti-FGG antibody (Abcam, Cambridge, UK).

[00348] A decrease in FGG mRNA expression in the HEPG2 cells is expected after transfection with the FGG ASO compared to FGG mRNA levels in HEPG2 cells transfected with the non-specific control ASO 48 hours after transfection. There is an expected decrease in the amount of FGG secreted protein, measured by quantifying the amount of FGG protein in media of HEPG2 cells transfected with the FGG ASO relative to the amount of FGG protein in media of HEPG2 cells transfected with a non-specific control ASO 48 hours after transfection. These results show that the FGG ASOs elicit knockdown of FGG mRNA in HEPG2 cells and that the decrease in FGG expression is correlated with a decrease in FGG protein secretion.

Example 6: Determining the activity of species cross-reactive siRNAs targeting FGG in mice

[00349] Five groups (n=4/group) of 8 week old male ICR mice (Harlan) were utilized in this study. On Study Day -4, all animals were anesthetized and blood was collected via the submandibular vein and into tubes containing citrate for collection of plasma. Plasma fibrinogen levels were measured using the Clauss method (IDEXX Laboratories, Test# 6308) and by ELISA according to the manufacturer's

instructions (Molecular Innovations Catalog# MFBGNKT). On Study Day 0, Group 1 mice were injected subcutaneously with 100 uL of sterile PBS, Group 2 mice were subcutaneously injected with 200 ug of ETD01592 (sense strand SEQ ID NO: 3591; antisense strand SEQ ID NO: 3595) in 100 uL of sterile PBS, Group 3 mice were subcutaneously injected with 200 ug ETD01593 (sense strand SEQ ID NO: 3592; antisense strand SEQ ID NO: 3596) in 100 uL of sterile PBS, Group 4 mice were subcutaneously injected with 200 ug of ETD01594 (sense strand SEQ ID NO: 3593; antisense strand SEQ ID NO: 3597) in 100 uL PBS, and Group 5 mice were subcutaneously injected with 200 ug of ETD01595 (sense strand SEQ ID NO: 3594; antisense strand SEQ ID NO: 3598) in 100 uL PBS. On Study Day 10, the animals from all Groups were anesthetized, bled via cardiac puncture to collect serum and plasma, and then euthanized. A liver sample was collected from all animals and placed in RNeasy Lysis Solution (Qiagen, Catalog# 69903). Serum clinical chemistry analyses were performed (IDEXX Laboratories, Test# 60513) and plasma fibrinogen levels were measured as described for the Day -4 samples. The liver samples were processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The relative level of FGG mRNA in each liver sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for mouse FGG (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1), and then normalized to the mean value of the control mice (Group 1) using the delta-delta Ct method.

[00350] The results of the liver mRNA analyses are shown in **Table 9**. Animals treated ETD01592 (Group 2), ETD01593 (Group 3), ETD01594 (Group 4), or ETD01595 (Group 4) showed decreased liver FGG mRNA levels compared with mice injected with PBS (Group 1). The results of the plasma fibrinogen analyses are shown in **Table 10**. Animals treated with ETD01592 (Group 2), ETD01593 (Group 3), ETD01594 (Group 4), or ETD01595 (Group 5) showed decreased plasma fibrinogen levels as measured by the Clauss method or by ELISA compared with mice injected with PBS (Group 1). The results from the clinical chemistry indicated all the siRNAs were generally well tolerated (**Table 11**).

Table 9: Day 10 FGG mRNA liver levels in mice treated with siRNAs targeting FGG

Group #	Treatment	Mouse #	Relative Liver FGG mRNA Level	Mean
1	PBS	1	0.933	1.00
		2	1.229	
		3	0.873	
		4	0.998	
2	ETD01592	5	0.098	0.13
		6	0.165	
		7	0.093	
		8	0.166	

3	ETD01593	9	0.201	0.22
		10	0.124	
		11	0.293	
		12	0.316	
4	ETD01594	13	0.148	0.14
		14	0.121	
		15	0.143	
		16	0.132	
5	ETD01595	17	0.095	0.16
		18	0.158	
		19	0.172	
		20	0.27	

Table 10. Day 10 plasma fibrinogen levels in mice treated with siRNAs targeting FGG

Group #	Treatment	Mouse #	Fibrinogen Plasma Level (Claus method, mg/dL)*	Relative Plasma Fibrinogen Level (ELISA)	Mean
1	PBS	1	2.840	1.21	1.00
		2	3.250	1.04	
		3	2.080	0.85	
		4	2.550	0.90	
2	ETD01592	5	<LLOQ	0.01	0.07
		6	<LLOQ	0.10	
		7	<LLOQ	0.09	
		8	<LLOQ	0.07	
3	ETD01593	9	<LLOQ	0.18	0.27
		10	<LLOQ	0.11	
		11	<LLOQ	0.52	
		12	0.490	0.27	
4	ETD01594	13	<LLOQ	0.13	0.14
		14	<LLOQ	0.11	
		15	<LLOQ	0.13	
		16	<LLOQ	0.20	
5	ETD01595	17	<LLOQ	0.20	0.23
		18	<LLOQ	0.16	
		19	<LLOQ	0.16	
		20	<LLOQ	0.39	

*Claus method LLOQ <0.5 mg/dL

Table 11. Clinical chemistry results after injection of mice with 200 ug of ETD01592, ETD01593, ETD01594 or ETD01595

Group #	Treatment	Mouse #	ALP (U/L)	AST (U/L)	ALT (U/L)	BUN (mg/dL)	CREAT (mg/dL)
1	PBS	1	79	122	42	31	0.2
		2	91	61	39	25	0.2
		3	64	141	66	34	0.2
		4	86	309	152	32	0

2	ETD01592	5	69	157	47	27	0.2
		6	74	90	76	29	0.2
		7	51	83	38	26	0.2
		8	102	91	40	27	0.2
3	ETD01593	9	100	174	46	29	0.2
		10	74	185	84	25	0.1
		11	103	78	63	27	0.2
		12	98	41	22	22	0.2
4	ETD01594	13	111	333	177	32	0.1
		14	61	53	22	27	0.2
		15	57	102	48	32	0.2
		16	105	486	107	28	0.2
5	ETD01595	17	114	129	43	33	0.2
		18	86	145	71	29	0.1
		19	80	170	95	28	0
		20	102	79	34	28	0.2

Example 7: Determining the activity of siRNAs targeting FG in mice at low dose levels

[00351] Nine groups (n=3/group) of 8 week old male ICR mice (Harlan) were utilized in this study. On Study Day 0, mice in Group 1 were injected subcutaneously with 100 uL of sterile PBS, mice in Groups 2 and 3 were subcutaneously injected with 20 ug or 60 ug of ETD01592, respectively (sense strand SEQ ID NO: 3591; antisense strand SEQ ID NO: 3595) in 100 uL of sterile PBS, mice in Groups 4 and 5 were subcutaneously injected with 20 ug or 60 ug of ETD01593, respectively (sense strand SEQ ID NO: 3592; antisense strand SEQ ID NO: 3596) in 100 uL of sterile PBS, mice in Groups 6 and 7 were subcutaneously injected with 20 ug or 60 ug of ETD01594, respectively (sense strand SEQ ID NO: 3593; antisense strand SEQ ID NO: 3597) in 100 uL PBS, and mice in Groups 8 and 9 were subcutaneously injected with 20 ug or 60 ug of ETD01595, respectively (sense strand SEQ ID NO: 3594; antisense strand SEQ ID NO: 3598) in 100 uL PBS. On Study Day 10, the animals from all groups were anesthetized, bled via cardiac puncture to collect serum and plasma, and then euthanized. A liver sample was collected from all animals and placed in RNeasy Lysis Solution (Qiagen, Catalog# 69903). Plasma fibrinogen levels were measured by ELISA according to the manufacturer's instructions (Molecular Innovations Catalog# MFBGNT). Plasma prothrombin time (PT) and activated partial thromboplastin time (aPTT) (IDEXX Laboratories, Test# 6308) and serum clinical chemistry measurements were also performed (IDEXX Laboratories, Test# 60513). The liver samples were processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The relative level of FG mRNA in each liver sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for mouse FG (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1), and then normalized to the mean value of the control mice (Group 1) using the delta-delta Ct method.

[00352] The results of the liver mRNA analyses are shown in **Table 12**. Animals treated with 20 ug ETD01592, ETD01593, ETD01594, or ETD01595 showed decreased liver FG mRNA levels compared

with mice injected with PBS. Animals treated with 60 ug ETD01592, ETD01593, ETD01594, or ETD01595 showed decreased liver FGG mRNA levels compared with mice injected with 20 ug of those siRNAs or with mice injected with PBS. The results of the plasma fibrinogen ELISA are shown in **Table 13**. Animals treated with 20 ug ETD01592, ETD01593, ETD01594, or ETD01595 showed decreased plasma fibrinogen protein levels compared with mice injected with PBS. Animals treated with 60 ug ETD01592, ETD01593, ETD01594, or ETD01595 showed decreased plasma fibrinogen protein levels compared with mice injected with 20 ug of those siRNAs or with mice injected with PBS. The results of the PT and aPTT measurements in animals treated with 20ug and 60ug ETD01592, ETD01593, ETD01594, or ETD01595 are shown in **Table 14**. The results from the clinical chemistry indicate that all the siRNAs were generally well tolerated at these dose levels (**Table 15**).

Table 12. FGG mRNA liver levels in mice treated with 20 ug or 60 ug of ETD01592, ETD01593, ETD01594 or ETD01595.

Group #	Treatment	Dose Level	Mouse #	Relative Liver FGG mRNA Level	Mean
1	PBS	NA	1	0.97	1.00
			2	1.07	
			3	0.97	
2	ETD01592	20 ug	4	0.90	0.80
			5	0.58	
			6	0.93	
3	ETD01592	60 ug	7	0.36	0.54
			8	0.57	
			9	0.70	
4	ETD01593	20 ug	10	1.10	1.12
			11	0.87	
			12	1.38	
5	ETD01593	60 ug	13	0.61	0.54
			14	0.42	
			15	0.58	
6	ETD01594	20 ug	16	0.69	0.78
			17	0.65	
			18	1.00	
7	ETD01594	60 ug	19	0.29	0.26
			20	0.36	
			21	0.11	
8	ETD01595	20 ug	22	0.64	0.86
			23	0.84	
			24	1.11	
9	ETD01595	60 ug	25	0.60	0.63
			26	0.58	
			27	0.71	

Table 13. Plasma fibrinogen levels in mice treated with 20 ug or 60 ug of ETD01592, ETD01593, ETD01594 or ETD01595.

Group #	Treatment	Dose Level	Mouse #	Relative Plasma Fibrinogen Level (ELISA)	Mean
1	PBS	NA	1	1.38	1.00
			2	1.00	
			3	0.62	
2	ETD01592	20 ug	4	0.83	0.61
			5	0.51	
			6	0.49	
3	ETD01592	60 ug	7	0.13	0.20
			8	0.21	
			9	0.27	
4	ETD01593	20 ug	10	0.53	0.54
			11	0.54	
			12	0.55	
5	ETD01593	60 ug	13	0.32	0.30
			14	0.46	
			15	0.11	
6	ETD01594	20 ug	16	0.50	0.28
			17	0.29	
			18	0.04	
7	ETD01594	60 ug	19	0.23	0.15
			20	0.20	
			21	0.03	
8	ETD01595	20 ug	22	0.63	0.58
			23	0.64	
			24	0.47	
9	ETD01595	60 ug	25	0.45	0.45
			26	0.39	
			27	0.51	

Table 14. PTT and aPTT in mice treated with 20 ug or 60 ug of ETD01592, ETD01593, ETD01594 or ETD01595.

Group #	Treatment	Dose Level	Mouse #	PT (s)	Mean (s)	aPTT (s)	Mean (s)
1	PBS	NA	1	11.6	11.4	23.9	28.0
			2	11.3		33.6	
			3	11.3		26.4	
2	ETD01592	20 ug	4	11.7	11.6	26.1	29.7
			5	11.5		33.8	
			6	11.6		29.2	
3	ETD01592	60 ug	7	14.1	13.4	22.5	24.8
			8	13.3		25.9	

			9	12.8		26	
4	ETD01593	20 ug	10	11.7	12.1	30.6	32.0
			11	12.1		24.2	
			12	12.5		41.3	
			13	11.4		20.3	
5	ETD01593	60 ug	14	12.3	12.8	50.9	33.3
			15	14.8		28.8	
			16	11.3		25.8	
6	ETD01594	20 ug	17	12.2	15.3	27.8	27.9
			18	22.3		30.1	
			19	17.6		23.9	
7	ETD01594	60 ug	20	13.2	19.8	26.4	47.2
			21	28.5		91.3	
			22	11.6		19.5	
8	ETD01595	20 ug	23	12.7	11.8	30.8	23.4
			24	10.9		19.9	
			25	11.7		21.4	
9	ETD01595	60 ug	26	11.4	11.9	29.4	25.8
			27	12.5		26.5	

Table 15. Clinical chemistry results after injection of mice with 20 ug or 60 ug of ETD01592, ETD01593, ETD01594 or ETD01595.

Group #	Treatment	Dose Level	Mouse #	ALP (U/L)	AST (U/L)	ALT (U/L)	BUN (mg/dL)	CREAT (mg/dL)
1	PBS	NA	1	77	83	32	22	0.1
			2	109	70	27	21	0.2
			3	118	65	30	22	0.1
2	ETD01592	20 ug	4	138	54	26	24	0.1
			5	93	55	26	25	0.1
			6	107	124	54	22	0.1
3	ETD01592	60 ug	7	100	67	25	18	0.1
			8	105	56	24	20	0.1
			9	69	64	23	19	0.1
4	ETD01593	20 ug	10	71	174	89	25	0.1
			11	99	67	31	22	0.1
			12	117	146	70	23	0.2
5	ETD01593	60 ug	13	110	69	30	27	0.2
			14	133	100	30	24	0.2
			15	119	46	26	31	0.1
6	ETD01594	20 ug	16	124	51	26	22	0.1
			17	126	235	158	24	0.1
			18	171	90	38	24	0.2
7	ETD01594	60 ug	19	72	54	32	20	0.1
			20	100	56	35	23	0.2

			21	114	135	50	31	0.2
8	ETD01595	20 ug	22	120	77	38	22	0.1
			23	93	387	102	28	0.2
			24	94	144	130	19	0.2
			25	93	72	23	21	0.1
9	ETD01595	60 ug	26	136	72	57	18	0.1
			27	135	51	22	25	0.2

Example 8: Inhibition of FGG in a Mouse Model for Depression Using Modified FGG siRNAs or ASOs.

[00353] In this experiment, a mouse model of depression is used to evaluate the effect of siRNA or ASO-mediated inhibition of FGG. To induce depression like symptoms the mice will be subjected to Chronic Social Defeat (CSD) by repeated social confrontations with an aggressive mouse for 15 consecutive days. Depression like symptoms are measured using Open Field Test, elevated T-maze and Tail Suspension Test.

[00354] Briefly, C57Bl/6J mice (Charles River, MA USA) are divided into six groups: Group 1 – a group treated with non-targeting control siRNA, Group 2 – a group treated with non-targeting control ASO, Group 3 – a group treated with FGG siRNA, Group 4 – a group treated with FGG ASO, Group 5 – a group treated with vehicle, Group 6 – a group not subjected to chronic social defeat, treated with vehicle. Each group contains 20 male mice.

[00355] Administration of siRNA or ASO is achieved with a 100ul subcutaneous injection of naked siRNA or ASO resuspended at concentration of 10 mg/mL in PBS. On Study Days 0, 7 and 21, Group 1 mice will be injected subcutaneously with non-targeting control siRNA, Group 2 mice will be injected subcutaneously with non-targeting control ASO, Group 3 mice will be injected subcutaneously with siRNA targeting mouse FGG, Group 4 mice will be injected subcutaneously with ASO targeting mouse FGG, and Group 5 and Group 6 mice will be injected subcutaneously with PBS.

[00356] All mice from groups 1-5 are exposed to CD-1/ICR mice (Charles River, MA USA), that have been previously screened for exhibiting aggressive behavior, for 15 days total beginning on Study Day 14. The behavioral tests are performed in Groups 1-5, 8 days after the final injection (Study Day 29).

[00357] Mice are first evaluated using the open field paradigm (44×44×40 cm) in a sound-attenuated room. The total distance (cm) traveled by each mouse is recorded for 5 min by a video surveillance system (SMART; Panlab SL, Barcelona, Spain) and is used to quantify activity levels. The floor of the open-field apparatus is cleaned with 10% ethanol between tests.

[00358] The elevated T-maze is a behavioral test useful for screening potential antidepressant drugs and assessing other manipulations that are expected to affect anxiety related behaviors. Mice are placed individually in an apparatus that consists of three elevated arms, one enclosed and two open. Mice will be initially placed in the enclosed arm of the maze and the time taken to leave the enclosed arm in three consecutive trials is measured. The total time in enclosed is recorded as an index of anxiety-like behavior.

[00359] The tail suspension test is a behavioral test useful for screening potential antidepressant drugs and assessing other manipulations that are expected to affect depression related behaviors. Mice are

suspended by their tail, without the ability to escape or reach the sides of the enclosure. During the duration of the test, 6 minutes, the mouse's escape-oriented behaviors will be quantified as well as time spent immobile. The total time spent attempting to escape versus time spent immobile is recorded as an index of depressive-like behavior.

[00360] 24 hours after the behavioral assessment, the mice are sacrificed by cervical dislocation following an intraperitoneal injection of 0.3 ml Nembutal (5 mg/ml) (Sigma Cat. No. 1507002). A liver sample will be collected from all animals and placed in RNeasy Lysis Buffer (Qiagen, Catalog# 69903). The liver samples will be processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The relative level of FGG mRNA in each liver sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for mouse FGG (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1), and then normalized to the mean value of the control mice using the delta-delta Ct method. Plasma fibrinogen levels will be measured use the Clauss method or by ELISA according to the manufacturer's instructions (Molecular Innovations Catalog# MFBGNKT).

[00361] A decrease in FGG mRNA expression in the liver tissue from mice dosed with the FGG siRNA or ASO is expected compared to FGG mRNA levels in the liver tissue from mice dosed with the non-specific controls. Measurement of plasma fibrinogen levels is expected to show a decrease in fibrinogen in the mice dosed with the FGG siRNA or ASO compared to fibrinogen from the plasma from mice dosed with non-specific control. There is an expected decrease in the time before the mice leave the enclosed arm of the elevated T-maze as well in a decrease in time spent in the enclosed arm in mice that receive the FGG siRNA or ASO compared to mice that receive non-specific control. In addition, there is an expected decrease in total immobility time in the tail suspension test along with no change in locomotor activity in the open field test in mice that receive the FGG siRNA or ASO compared to mice that receive non-specific control.

Example 9: Inhibition of FGG in a mouse model for Alzheimer's disease using FGG siRNAs or ASOs

[00362] In this experiment, a mouse model of Alzheimer's disease using 5xFAD mice which express human APP and PSEN1 transgenes with a total of five AD-linked mutations is used to evaluate the effect of siRNA or ASO inhibition of FGG. Cognitive function is measured using a contextual fear conditioning (CFC).

[00363] Briefly, 7-month-old 5xFAD mice are divided into five groups: Group 1 – a group treated with non-targeting control siRNA, Group 2 – a group treated with non-targeting control ASO, Group 3 – a group treated with FGG siRNA1, Group 4 – a group treated with FGG ASO1, Group 5 – a group treated with vehicle. Each group contains 20 mice.

[00364] Administration of siRNA or ASO is achieved with a 100ul subcutaneous injection of GalNAc-conjugated siRNA or ASO at concentration of 10 mg/mL in PBS. On Study Days 0, 7 and 14, Group 1 mice will be injected subcutaneously with non-targeting control siRNA, Group 2 mice will be injected subcutaneously with non-targeting control ASO, Group 3 mice will be injected subcutaneously with siRNA1 targeting mouse FGG, Group 4 mice will be injected subcutaneously with ASO1 targeting mouse FGG, and Group 5 mice will be injected subcutaneously with vehicle. The behavioral tests are performed 7 days after the final injection.

[00365] To rule out nonspecific motor effects that could influence the results of the cognitive function tests, the potential effect of siRNA or ASO treatment on locomotor activity is assessed. Mice are evaluated using the openfield paradigm (44×44×40 cm) in a sound-attenuated room. The total distance (cm) traveled by each mouse is recorded for 5 min by a video surveillance system (SMART; Panlab SL, Barcelona, Spain) and is used to quantify activity levels. The floor of the open-field apparatus is cleaned with 10% ethanol between tests.

[00366] Mice are then evaluated using the contextual fear conditioning (CFC) and active avoidance (AA) paradigms. Mice are subjected to repeated electric shock stimuli in a sound-attenuated room over multiple trials. The freezing and avoidance behaviors are recorded for each trial by a video surveillance system (SMART; Panlab SL, Barcelona, Spain) and are used to quantify freezing time and avoidance. The floor of the apparatus is cleaned with 10% ethanol between tests.

[00367] 24 hours after the behavioral assessment, the mice are sacrificed by cervical dislocation following an intraperitoneal injection of 0.3 ml Nembutal (5 mg/ml) (Sigma Cat. No. 1507002). A liver sample will be collected from all animals and placed in RNeasy Lysis Solution (Qiagen) and placed in RNeasy Lysis Solution (ThermoFisher, Catalog# AM7020). The liver samples will be processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The relative level of FGG mRNA in each liver sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for mouse FGG (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1), and then normalized to the mean value of the control mice using the delta-delta Ct method. Plasma fibrinogen levels will be measured use the Clauss method or by ELISA according to the manufacturer's instructions (Molecular Innovations Catalog# MFBGNKT).

[00368] A decrease in FGG mRNA expression in the liver tissue from mice dosed with the FGG siRNA or ASO is expected compared to FGG mRNA levels in the liver tissue from mice dosed with the non-specific controls. Measurement of plasma fibrinogen levels is expected to show a decrease in fibrinogen in the mice dosed with the FGG siRNA or ASO compared to fibrinogen from the plasma from mice dosed with non-specific control. There is an expected decrease in freezing time in the CFC and increase in the avoidance behaviors in the AA in mice that receive the FGG siRNA or ASO compared to

mice that receive the non-specific controls along with no change between treatment groups in the locomotor activity test.

Example 10: Screening FGG siRNAs for activity in Huh7 cells in culture

[00369] Chemically modified FGG siRNAs cross-reactive for at least human and non-human primates were assayed for FGG mRNA knockdown activity in cells in culture. Huh7 cells (Xenotech catalog# JCRB0403) were seeded in 96-well tissue culture plates at a cell density of 20,000 cells per well in DMEM media (VWR catalog# 02-0100-0500) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere containing 5% carbon dioxide. The FGG siRNAs were individually transfected into Huh7 cells in duplicate wells at 1 nM and 10 nM final concentration using 0.2 µL Lipofectamine RNAiMax (Fisher, catalog# 13778150) in 5 µL Opti-MEM (Thermo Fisher, catalog# 31985070) per well. Silencer Select Negative Control #1 (ThermoFisher, catalog# 4390843) was transfected at 1 nM and 10 nM final concentrations as a negative control. Positive control siRNAs targeting FGG (ThermoFisher, catalog# 4392420, Assay IDs s5179, s5180) were transfected at 1 nM and 10 nM final concentrations. After incubation for 48 hours at 37°C, total RNA was harvested from each well using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, catalog# A35374) according to the manufacturer's instructions. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The level of FGG mRNA from each well was measured in triplicate by biplex real-time qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan® Fast Advanced Master Mix (Fisher Scientific catalog# 44-445-58), TaqMan Gene Expression Assay for human FGG (ThermoFisher, assay# Hs00241037_m1) and TaqMan Gene Expression Assay for human PPIA (ThermoFisher, assay# Hs99999904_m1). The relative FGG mRNA levels in each well was calculated using the delta-delta Ct method. All data were normalized to relative FGG mRNA levels in untreated Huh7 cells. Results are shown in Table 16.

Table 16: Knockdown activity of FGG-specific siRNAs at 1 nM and 10 nM in Huh7 cells

			Relative Activity	
Untreated Cells	-	-	1.00	
siRNA name	Sense Strand SEQ ID NO	Antisense Strand SEQ ID NO	10 nM siRNA	1 nM siRNA
Neg. Ctrl siRNA	-	-	0.96	1.00
Pos. Ctrl siRNA-1	-	-	0.09	0.34
Pos. Ctrl siRNA-2	-	-	0.13	0.58
ETD01663	3485	3538	0.19	0.51
ETD01664	3486	3539	0.21	0.56
ETD01665	3487	3540	0.18	0.41
ETD01666	3488	3541	0.15	0.66
ETD01667	3489	3542	0.64	0.87
ETD01668	3490	3543	0.32	0.66
ETD01669	3491	3544	0.39	0.63
ETD01670	3492	3545	0.10	0.47

ETD01671	3493	3546	0.65	0.73
ETD01672	3494	3547	0.36	0.98
ETD01673	3495	3548	0.46	0.80
ETD01674	3496	3549	0.26	0.92
ETD01675	3497	3550	0.48	0.86
ETD01676	3498	3551	0.49	0.92
ETD01677	3499	3552	0.35	0.89
ETD01678	3500	3553	0.36	0.69
ETD01679	3501	3554	0.44	0.95
ETD01680	3502	3555	0.31	0.96
ETD01681	3503	3556	0.26	0.71
ETD01682	3504	3557	0.70	0.97
ETD01683	3505	3558	0.32	0.87
ETD01684	3506	3559	0.52	0.87
ETD01685	3507	3560	0.27	0.87
ETD01686	3508	3561	0.14	0.51
ETD01687	3509	3562	0.47	0.85
ETD01688	3510	3563	0.45	0.94
ETD01689	3511	3564	0.97	0.74
ETD01690	3512	3565	0.32	0.90
ETD01691	3513	3566	0.52	0.98
ETD01692	3514	3567	0.47	0.89
ETD01693	3515	3568	0.42	0.92
ETD01694	3516	3569	0.05	0.50
ETD01695	3517	3570	0.57	0.84
ETD01696	3518	3571	0.27	0.97
ETD01697	3519	3572	0.20	0.65
ETD01698	3520	3573	0.25	1.12
ETD01699	3521	3574	0.39	0.95
ETD01700	3522	3575	0.34	0.89
ETD01701	3523	3576	0.16	0.84
ETD01702	3524	3577	0.33	0.63
ETD01703	3525	3578	0.19	0.52
ETD01704	3526	3579	0.25	0.88
ETD01705	3527	3580	0.31	0.79
ETD01706	3528	3581	0.99	1.02
ETD01707	3529	3582	0.26	0.89
ETD01708	3530	3583	0.80	0.75
ETD01709	3531	3584	0.26	0.81
ETD01710	3532	3585	0.17	0.64
ETD01711	3533	3586	0.44	0.41
ETD01712	3534	3587	0.46	0.64
ETD01713	3535	3588	0.23	0.68
ETD01714	3536	3589	0.45	0.80

ETD01715	3537	3590	0.45	0.94
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Example 11: Determining the IC₅₀ of FGG siRNAs in Huh7 cells in culture

[00370] The IC₅₀ values for knockdown of FGG mRNA by select FGG siRNAs were determined in Huh7 cells. The siRNAs were assayed individually in triplicate at 30 nM, 10 nM, 3 nM, 1 nM and 0.3 nM, 0.1 nM and 0.03 nM. Huh7 cells (Xenotech catalog# JCRB0403) were seeded in 96-well tissue culture plates at a cell density of 20,000 cells per well in DMEM media (VWR catalog# 02-0100-0500) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere supplemented with 5% carbon dioxide. The FGG siRNAs will be individually transfected using 0.2 µL Lipofectamine RNAiMax (Fisher, catalog# 13778150) in 5 uL Opti-MEM (Thermo Fisher, catalog# 31985070) per well. The positive control siRNA targeting FGG (ThermoFisher, catalog# 4392420, Assay ID s5179) was included as a comparator. After incubation for 48 hours at 37°C, total RNA was harvested from each well using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, catalog# A35374) according to the manufacturer's instructions. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The level of FGG mRNA from each well was measured in triplicate by biplex real-time qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan® Fast Advanced Master Mix (Fisher Scientific catalog# 44-445-58), TaqMan Gene Expression Assay for human FGG (ThermoFisher, assay# Hs00241037_m1) and TaqMan Gene Expression Assay for human PPIA (ThermoFisher, assay# Hs99999904_m1). The relative FGG mRNA levels in each well was calculated using the delta-delta Ct method. All data were normalized to relative FGG mRNA levels in untreated Huh7 cells. Curve fit was accomplish using the [inhibitor] vs. response (three parameters) function in GraphPad Prism software. Results are shown in **Table 17**.

Table 17. IC₅₀ Values of FGG siRNAs in Human Huh7 Cells

		Relative FGG mRNA Levels	
Untreated Cells		1.00	
siRNA	[siRNA]		IC ₅₀ (nM)
Pos. Ctrl siRNA-1	30 nM	0.16	5.6
	10 nM	0.35	
	3 nM	0.41	
	1 nM	0.81	
	0.3 nM	0.83	
	nM	0.64	
	0.03 nM		
ETD01663	30 nM	0.49	20.3
	10 nM	0.87	
	3 nM	1.05	
	1 nM	1.34	
	0.3 nM	1.42	
	0.1 nM	1.10	
	0.03 nM	1.32	
ETD01665	30 nM	0.43	1.9
	10 nM	0.53	
	3 nM	0.77	
	1 nM	0.99	

	0.3 nM	1.16	
	0.1 nM	1.04	
	0.03 nM	1.49	
ETD01666	30 nM	0.28	17.0
	10 nM	0.68	
	3 nM	1.02	
	1 nM	1.23	
	0.3 nM	1.29	
	0.1 nM	0.84	
	0.03 nM	1.54	
ETD01670	30 nM	0.33	15.6
	10 nM	0.87	
	3 nM	1.11	
	1 nM	1.15	
	0.3 nM	1.41	
	0.1 nM	1.33	
	0.03 nM	1.60	
ETD01686	30 nM	0.29	4.9
	10 nM	0.72	
	3 nM	1.07	
	1 nM	1.44	
	0.3 nM	1.72	
	0.1 nM	1.85	
	0.03 nM	1.59	
ETD01694	30 nM	0.47	21.1
	10 nM	1.10	
	3 nM	1.31	
	1 nM	1.63	
	0.3 nM	1.88	
	0.1 nM	1.64	
	0.03 nM	1.61	
ETD01697	30 nM	0.39	6.6
	10 nM	1.14	
	3 nM	1.18	
	1 nM	1.81	
	0.3 nM	2.07	
	0.1 nM	2.04	
	0.03 nM	1.89	
ETD01701	30 nM	0.45	30.4
	10 nM	1.12	
	3 nM	1.62	
	1 nM	1.76	
	0.3 nM	1.88	
	0.1 nM	1.68	
	0.03 nM	1.88	
ETD01703	30 nM	0.29	25.8
	10 nM	0.66	
	3 nM	0.87	
	1 nM	1.45	
	0.3 nM	1.00	
	0.1 nM	1.00	
	0.03 nM	1.09	
ETD01710	30 nM	0.17	4.2
	10 nM	0.44	
	3 nM	0.70	

	1 nM	0.91	
	0.3 nM	1.09	
	0.1 nM	1.16	
	0.03 nM	1.16	

Example 12. Optimization of siRNAs targeting human, cynomologus monkey, rat and mouse *FGG* in mice

[00371] Several siRNAs designed to be cross-reactive with human, cynomologus monkey and mouse *FGG* mRNA were tested for activity in mice. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in **Table 18**, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage.

[00372] Six to eight week old female mice (strain ICR, n=4) were given a subcutaneous injection on Day 0 of a single 20ug or 60ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00373] Mice were euthanized on Day 14 after injection and a liver sample from each was collected and placed in RNAlater (ThermoFisher Catalog# AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *FGG* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Results are shown in **Table 19**.

[00374] On Day 0 (prior to dosing), 7 and Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 20**.

[00375] On Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 21**.

Table 18A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5’-3’) with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5’-3’)
ETD01818	3650	[ETL17]sgaugAfAfaGfAfuucggaguasusu	3686	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01839	3652	[ETL17]sgaugAfAfaGfAfuucggaguasusu	3688	usAfscuaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01840	3653	[ETL17]sgaugAfAfaGfAfuucggaguasusu	3689	usAfscUfaceGfaAfuCfuUfuCfaUfcsusu
ETD01841	3654	[ETL17]sgaugAfAfaGfAfuucggaguasusu	3690	usAfscUfacCfgaAfuCfuUfuCfaUfcsusu

Table 18B. Example siRNA BASE Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01818	3722	UACCAAGGTGGCACUUACA	3758	UACUACCGAAUCUUUCAUC
ETD01839	3724	GAUGAAAGAUUCGGUAGUA	3760	UACUACCGAAUCUUUCAUC
ETD01840	3725	UGACAAGUUUUUCACAUCA	3761	UACUACCGAAUCUUUCAUC
ETD01841	3726	GAAGAUUCAUUUGAUAGA	3762	UACUACCGAAUCUUUCAUC

Table 19. Relative *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean <i>FGG</i> mRNA (Normalized to Group 1, Day 14)
1	4	PBS	0	1.00375
2	4	ETD01818	20	0.90475
3	4	ETD01818	60	0.41
4	4	ETD01839	20	0.5715
5	4	ETD01839	60	0.317
6	4	ETD01840	20	0.70675
7	4	ETD01840	60	0.2125
8	4	ETD01841	20	0.4445
9	4	ETD01841	60	0.246

Table 20. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting *FGG*

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)		
				Day 0	Day 7	Day 14
1	4	PBS	0	1	1.211	0.732
2	4	ETD01818	20	1	0.832	0.531
3	4	ETD01818	60	1	0.478	0.245
4	4	ETD01839	20	1	0.436	0.395
5	4	ETD01839	60	1	0.186	0.142
6	4	ETD01840	20	1	0.555	0.645
7	4	ETD01840	60	1	0.433	0.402
8	4	ETD01841	20	1	0.541	0.371
9	4	ETD01841	60	1	0.157	0.180

Table 21. PT and APTT Times in Mice treated with siRNAs targeting *FGG*

Group	n	Treatment	Dose (ug)	Mean <i>PT</i> (sec) Day 14	Mean <i>APTT</i> (sec) Day 14
1	4	PBS	0	17.4	47.6
2	4	ETD01818	20	18.375	43.875
3	4	ETD01818	60	24.875	64.8
4	4	ETD01839	20	18.225	46.075
5	4	ETD01839	60	20.425	45.325
6	4	ETD01840	20	15.65	28.3
7	4	ETD01840	60	19.625	50.725
8	4	ETD01841	20	21.375	41.875

9	4	ETD01841	60	31.575	47.233
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Example 13. Optimization of siRNAs from position 1218 targeting human, cynomolgus monkey, rat and mouse *FGG* in mice

[00376] Several siRNAs designed to be cross-reactive with human, cynomolgus monkey and mouse *FGG* mRNA were tested for activity in mice. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in **Table 22A**, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage.

[00377] Six to eight week old female mice (strain ICR, n=4) were given a subcutaneous injection on Day 0 of a single 60ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00378] Mice were euthanized on Day 10 after injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *FGG* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Results are shown in **Table 23**.

[00379] On Day 0 (prior to dosing), 7 and Day 10 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 24**.

[00380] On Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 25**.

Table 22A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5’-3’) with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5’-3’)
ETD01841	3654	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	369	usApscUfacCfgaAfuCfuUfuCfaUfcsusu
ETD01852	3658	[ETL17]sugacaagUfUfUfUfucacaucasusu	3694	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01921	3670	[ETL17]sugacaagUfUfUfUfucacaucasusu	3706	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01922	3671	[ETL17]sugacaaguUfUfUfUfucacaucasusu	3707	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01923	3672	[ETL17]sugacaagUfUfUfUfucacaucasusu	3708	usGfsaugUfgAfaAfaAfcUfuGfuCfasusu
ETD01924	3673	[ETL17]sugacaagUfUfUfUfucacaucasusu	3709	usGfsaUfgUfgaaAfaAfcUfuGfuCfasusu
ETD01925	3674	[ETL17]sugacaagUfUfUfUfucacaucasusu	3710	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01926	3675	[ETL17]sugacaagUfUfUfUfucacaucasusu	3711	usGfsaUfgUfgaaaaAfcUfuGfuCfasusu
ETD01927	3676	[ETL17]sugacaagUfUfUfUfucacaucasusu	3712	usGfsaugUfgAfaaaAfcUfuGfuCfasusu

Table 22B. Example siRNA BASE Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01841	3726	GAAGAUUCAUUUGAUAAGA	3762	UACUACCGAAUCUUUCAUC
ETD01852	3730	UACCAAGGTGGCACUUACA	3766	UGAUGUGAAAAACUUGUCA
ETD01921	3742	GAUGAAAGAUUCGGUAGUA	3778	UGAUGUGAAAAACUUGUCA
ETD01922	3743	GAUGAAAGAUUCGGUAGUA	3779	UGAUGUGAAAAACUUGUCA
ETD01923	3744	GAUGAAAGAUUCGGUAGUA	3780	UGAUGUGAAAAACUUGUCA
ETD01924	3745	GAUGAAAGAUUCGGUAGUA	3781	UGAUGUGAAAAACUUGUCA
ETD01925	3746	CUCAAUGGAGUUUAUUACA	3782	UGAUGUGAAAAACUUGUCA
ETD01926	3747	UGACAAGUUUUUCACAUCA	3783	UGAUGUGAAAAACUUGUCA
ETD01927	3748	UCAAUGGAGUUUAUUACCA	3784	UGAUGUGAAAAACUUGUCA

Table 23. Relative *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean <i>FGG</i> mRNA (Normalized to Group 1, Day 10)
1	4	PBS	0	1.01025
2	4	ETD01841	60	0.436
3	4	ETD01852	60	0.91125
4	4	ETD01921	60	0.788
5	4	ETD01922	60	1.384
6	4	ETD01923	60	0.98975
7	4	ETD01924	60	0.85675
8	4	ETD01925	60	0.7335
9	4	ETD01926	60	0.57025
10	4	ETD01927	60	0.73425

Table 24. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting *FGG*

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)		
				Day 0	Day 7	Day 10
1	4	PBS	0	1	1.38	1.32
2	4	ETD01841	60	1	0.65	0.52
3	4	ETD01852	60	1	1.17	0.68
4	4	ETD01921	60	1	0.95	0.69
5	4	ETD01922	60	1	0.93	0.93
6	4	ETD01923	60	1	1.08	0.97
7	4	ETD01924	60	1	0.85	0.68
8	4	ETD01925	60	1	0.82	0.60
9	4	ETD01926	60	1	0.50	0.31
10	4	ETD01927	60	1	0.51	0.58

Table 25. PT and APTT Times in Mice treated with siRNAs targeting *FGG*

Group	n	Treatment	Dose (ug)	Mean PT (sec) Day 10	Mean APPT (sec) Day 10
1	4	PBS	0	14.15	34.97
2	4	ETD01841	60	31.85	37.07
3	4	ETD01852	60	15.55	31.97
4	4	ETD01921	60	15.825	42.83
5	4	ETD01922	60	16.05	32.23

6	4	ETD01923	60	15.55	46.4
7	4	ETD01924	60	15.075	35.13
8	4	ETD01925	60	16.57	34.03
9	4	ETD01926	60	16.775	35.78
10	4	ETD01927	60	16.075	45.6

Example 14. Testing differentially modified GalNAc siRNAs targeting human, cynomolgus monkey, rat and mouse *FGG* in mice

[00381] Several siRNAs designed to be cross-reactive with human, cynomolgus monkey and mouse *FGG* mRNA were tested for activity in mice. The siRNAs were attached to the GalNAc ligand ETL1 or ETL17. The siRNA sequences are shown in **Table 26A**, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage.

[00382] Six to eight week old female mice (strain ICR, n=4) were given a subcutaneous injection on Day 0 of a single 60ug or 120ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00383] Mice were euthanized on Day 14 after injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *FGG* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Results are shown in **Table 27**.

[00384] On Day 0 (prior to dosing), 7 and Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 28**.

[00385] On Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 29**. Mice injected with ETD01811, ETD01818, and ETD01819 had an increase in PT and APTT times on Day 7 and 14 relative to mice receiving PBS.

[00386] On Days 0, 7, and 14 blood was collected into tubes with no anti-coagulant serum collected. Clinical chemistry parameters containing ALT, ALP, TBIL, and BUN were analyzed at IDEXX Laboratories (IDEXX Laboratories, Test# 62849). Results are shown in **Table 30**.

Table 26A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5'-3') with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5'-3')
ETD01811	3649	[ETL1]sgaugAfAfaGfAfuucgguaguasusu	3685	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01818	3650	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3686	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01819	3651	[ETL17]sgaagAfuucAfuugauaagasu	3687	usCfsuUfaUfcAfaAfuGfaAfuCfuUfcsusu

Table 26B. Example siRNA Base Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01811	3721	UGACAAGUUUUUACAUC	3757	UACUACCGAAUCUUUCAUC
ETD01818	3722	UACCAAGGTGGCACUUACA	3758	UACUACCGAAUCUUUCAUC
ETD01819	3723	UGACAAGUUUUUACAUC	3759	UCUUAUCAAUGAAUCUUC

Table 27. Relative FGG mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean FGG mRNA (Normalized to Group 1, Day 14)
1	4	PBS	0	1.00
2	4	ETD01811	60	0.23
3	4	ETD01811	120	0.14
4	4	ETD01818	60	0.17
5	4	ETD01818	120	0.14
6	4	ETD01819	120	0.16

Table 28. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)		
				Day 0	Day 7	Day 14
1	4	PBS	0	1	1.03	0.74
2	4	ETD01811	60	1	0.20	0.18
3	4	ETD01811	120	1	0.13	0.06
4	4	ETD01818	60	1	0.16	0.12
5	4	ETD01818	120	1	0.11	0.08
6	4	ETD01819	120	1	0.23	0.14

Table 29. PT and APTT Times in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean PT (sec) Day 14	Mean APPT (sec) Day 14
1	4	PBS	0	14	39.45
2	4	ETD01811	60	18.4	57.675
3	4	ETD01811	120	46.4	83.425
4	4	ETD01818	60	21.3	61.825
5	4	ETD01818	120	27	59.325
6	4	ETD01819	120	18.675	43.525

Table 30. Clinical Chemistry in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	ALT (U/L) Day 14	ALP (U/L) Day 14	TBILI (mg/dL) Day 14	BUN (mg/dL) Day 14
1	4	PBS	0	98.25	91.75	0.1	21.25
2	4	ETD01818	20	53.75	106.75	0.1	22.5
3	4	ETD01818	60	72	60	0.1	21.5
4	4	ETD01839	20	39.25	75	0.125	24
5	4	ETD01839	60	25	90.25	0.1	19
6	4	ETD01840	20	25.75	90	0.15	22.75

Example 15. Screening siRNAs from position 352 targeting human, cynomologus monkey, rat and mouse *FGG* in mice

[00387] Several siRNAs designed to be cross-reactive with human, cynomologus monkey and mouse *FGG* mRNA were tested for activity in mice. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in **Table 31A**, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, “d” is a deoxynucleoside, and “s” is a phosphorothioate linkage.

[00388] Six to eight week old female mice (strain ICR, n=3) were given a subcutaneous injection on Day 0 of a single 40ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control. Mice were euthanized on Day 14 after injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *FGG* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Results are shown in **Table 32**.

Table 31A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5’-3’) with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5’-3’)
ETD01818	3650	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3686	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01918	3667	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3703	usAfsucaCfcgaAfuCfuUfuCfaUfcsusu
ETD01919	3668	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3704	dTsAfsucaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01920	3669	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3705	UfsAfsucaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01870	3664	[ETL17]sagguggCfaCfUfuacucaaaasusu	3700	usAfsdcdTadCcGfaAfuCudTudCadTcsusu
ETD01869	3665	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3701	usAfsdcdTadCcGfaAfuCfuUfuCfaUfcsusu

Table 31B. Example siRNA Base Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01818	3722	UACCAAGGTGGCACUUACA	3758	UACUACCGAAUCUUUCAUC
ETD01918	3739	GAUGAAAGAUUCGGUAGUA	3775	UACUACCGAAUCUUUCAUC
ETD01919	3740	GAUGAAAGAUUCGGUAGUA	3776	TACUACCGAAUCUUUCAUC
ETD01920	3741	GAUGAAAGAUUCGGUAGUA	3777	UACUACCGAAUCUUUCAUC
ETD01870	3738	GAAGAUUCAUUUGAUAAAGA	3774	UACTACCGAAUCUTUCATC
ETD01869	3737	GAUGAAAGAUUCGGUAGUA	3773	UACTACCGAAUCUUUCAUC

Table 32. Relative *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean <i>FGG</i> mRNA (Normalized to Group 1, Day 14)
1	3	PBS	0	1.00
2	3	ETD01818	40	0.66
3	3	ETD01918	40	0.40
4	3	ETD01919	40	1.06
5	3	ETD01920	40	1.10
6	3	ETD01870	40	1.71
7	3	ETD01869	40	0.71

Example 16. Screening siRNAs from siRCHv2 targeting human, cynomologus monkey, rat and mouse *FGG* in mice

[00389] Several siRNAs designed to be cross-reactive with human, cynomologus monkey and mouse *FGG* mRNA were tested for activity in mice. The siRNAs were attached to the GalNAc ligand ETL1 or ETL17. The siRNA sequences are shown in **Table 33A**, where “Nf” is a 2' fluoro-modified nucleoside, “n” is a 2' O-methyl modified nucleoside, “d” is a deoxynucleoside, and “s” is a phosphorothioate linkage.

[00390] Six to eight week old female mice (strain ICR, n=3) were given a subcutaneous injection on Day 0 of a single 60ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00391] Mice were euthanized on Day 10 after injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver *FGG* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Results are shown in **Table 34**.

[00392] On Day 0 (prior to dosing), Day 10 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 35**.

[00393] On Day 10 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 36**.

Table 33A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5'-3') with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5'-3')
ETD01818	3650	[ETL17]sgaugAfAfaGfAfuucgguaguasusu	3686	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01808	3647	[ETL1]scucaAfuGfGfAfGfuuuuuuacacusu	3683	usGfsuAfaUfaAfaCfuCfcAfuUfgAfgsusu
ETD01809	3648	[ETL1]sucaauGfGfAfGfuuuuuuacacusu	3684	usGfsgUfaAfuAfaAfcUfcCfaUfuGfasusu
ETD01849	3655	[ETL17]sagacaUfCfaUfgaguuggucasusu	3691	usGfsaCfcAfaCfuCfaUfgAfuGfuCfususu
ETD01851	3656	[ETL17]sagacuGfGfAfAfuGfgcagaacacusu	3692	usGfsuUfcUfgCfcAfuUfcCfaGfuCfususu
ETD01852	3657	[ETL17]sugacaagUfUfUfUfucacacacusu	3693	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01853	3658	[ETL17]sugacaagUfUfUfUfucacacacusu	3694	usGfsgAfuGfuGfaAfaAfaCfuUfgUfcsusu
ETD01855	3659	[ETL17]sgacaagUfUfUfUfucacacacusu	3695	usCfsaCfcUfuGfgUfaAfuAfaAfcUfcsusu
ETD01856	3660	[ETL17]sgaguUfUfaUfUfaCfcaaggugasusu	3696	usGfsuAfaGfuGfcCfaCfcUfuGfgUfasusu
ETD01857	3661	[ETL17]suaccAfaGfGfdTggcacuuacacusu	3697	usAfsgUfaAfgUfgCfcAfcCfuUfgGfususu
ETD01858	3662	[ETL17]saccaAfGfguGfGfcacuuacacusu	3698	usUfsuGfaGfuAfaGfuGfcCfaCfcUfususu
ETD01859	3663	[ETL17]saagguGfGfcAfcuuacucacacusu	3699	usUfsuUfgAfgUfaAfgUfgCfcAfcCfususu

Table 33B. Example siRNA Base Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01818	3722	UACCAAGGTGGCACUUACA	3758	UACUACCGAAUCUUUCAUC
ETD01808	3719	UGACAAGUUUUUCACAUCA	3755	UGUAAUAAACUCCAUUGAG
ETD01809	3720	UGACAAGUUUUUCACAUCA	3756	UGGUAAUAAACUCCAUUGA
ETD01849	3727	GAUGAAAGAUUCGGUAGUA	3763	UGACCAACUCAUGAUGUCU
ETD01851	3728	AGACAUCAUGAGUUGGUCA	3764	UGUUCUGCCAUUCCAGUCU
ETD01852	3729	GACAAGUUUUUCACAUCCA	3765	UGAUGUGAAAAACUUGUCA
ETD01853	3730	UACCAAGGTGGCACUUACA	3766	UGGAUGUGAAAAACUUGUC
ETD01855	3731	ACCAAGGUGGCACUUACUA	3767	UCACCUUGGUAAUAAACUC
ETD01856	3732	UGACAAGUUUUUCACAUCA	3768	UGUAAGUGCCACCUUGGUA
ETD01857	3733	GAUGAAAGAUUCGGUAGUA	3769	UAGUAAGUGCCACCUUGGU
ETD01858	3734	GAUGAAAGAUUCGGUAGUA	3770	UUUGAGUAAGUGCCACCUU
ETD01859	3735	UGACAAGUUUUUCACAUCA	3771	UUUUGAGUAAGUGCCACCU

Table 34. Relative *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean <i>FGG</i> mRNA (Normalized to Group 1, Day 10)
1	3	PBS	0	1.00
2	3	ETD01818	60	0.22
3	3	ETD01808	60	1.12
4	3	ETD01809	60	1.00
5	3	ETD01849	60	0.64
6	3	ETD01851	60	0.53
7	3	ETD01852	60	0.33
8	3	ETD01853	60	0.69

9	3	ETD01855	60	0.96
10	3	ETD01856	60	0.77
11	3	ETD01857	60	0.71
12	3	ETD01858	60	0.91
13	3	ETD01859	60	1.00

Table 35. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)	
				Day 0	Day 10
1	3	PBS	0	1.00	0.96
2	3	ETD01818	60	1.00	0.34
3	3	ETD01808	60	1.00	0.38
4	3	ETD01809	60	1.00	0.53
5	3	ETD01849	60	1.00	0.42
6	3	ETD01851	60	1.00	0.80
7	3	ETD01852	60	1.00	0.96
8	3	ETD01853	60	1.00	0.34
9	3	ETD01855	60	1.00	0.38
10	3	ETD01856	60	1.00	0.53
11	3	ETD01857	60	1.00	0.42
12	3	ETD01858	60	1.00	0.80
13	3	ETD01859	60	1.00	0.96

Table 36. PT and APTT Times in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean PT (sec) Day 14	Mean APPT (sec) Day 14
1	3	PBS	0	16.17	35.10
2	3	ETD01818	60	18.40	32.33
3	3	ETD01808	60	17.30	47.60
4	3	ETD01809	60	17.83	49.57
5	3	ETD01849	60	21.27	44.50
6	3	ETD01851	60	43.73	18.97
7	3	ETD01852	60	48.83	18.10
8	3	ETD01853	60	34.15	52.45
9	3	ETD01855	60	18.20	45.50
10	3	ETD01856	60	16.00	43.93
11	3	ETD01857	60	15.90	48.67
12	3	ETD01858	60	24.60	55.85
13	3	ETD01859	60	17.43	39.13

Example 17. Screening of siRNAs from positions 352 and 1218 targeting human FGG mRNA in mice transfected with AAV8-TBG-h-FGG

[00394] Several siRNAs designed to be cross-reactive with human, cynomolgus monkey, rat and mouse *FGG* mRNA were tested for activity in mice following transfection with an adeno-associated viral vector. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in

Table 37A, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, “d” is a deoxynucleoside, and “s” is a phosphorothioate linkage.

[00395] Six to eight week old female mice (C57Bl/6) were injected with 10 uL of a recombinant adeno-associated virus 8 (AAV8) vector (2.1×10^{13} genome copies/mL) by the retroorbital route on Day -14. The recombinant AAV8 contains the open reading frame and a portion of the 5’ and 3’UTRs of the human FG sequence (ENST00000404648) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-FG). On Day 0, infected mice (n=3) were given a subcutaneous injection of a single 60 ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00396] Mice were euthanized on Day 14 after subcutaneous injection and a liver sample from each was collected and placed in RNeasy (ThermoFisher Catalog# AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *MTRES1* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for human *FG* (ThermoFisher, assay# Hs00241038_m1), or mouse *FG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FG* mRNA level in animals receiving PBS. Mice injected with ETD01592, ETD01594, ETD01745, ETD01747, ETD01748, and ETD01750 had substantial reductions in mean liver mouse *FG* mRNA on Day 14 relative to mice receiving PBS. Results are shown in **Table 38**. Mice injected with ETD01592, ETD01594, ETD01745, ETD01747, ETD01748, and ETD01750 had substantial reductions in mean liver human *FG* mRNA on Day 14 relative to mice receiving PBS. Results are shown in **Table 39**.

[00397] On Day 0 (prior to dosing), 7 and Day 10 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 40**.

[00398] On Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 41**. On average mice injected with ETD01592, ETD01594, ETD01745, ETD01747, ETD01748, and ETD01750 had no change in PT and APPT times on Day 14 relative to mice receiving PBS.

Table 37A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5’-3’) with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5’-3’)
ETD01592	3641	[ETL1]gsasugAfAfaGfAfuucgguaguasuu	3677	usAfscUfaCfcGfaAfuCfuUfuCfaUfcusu

ETD01594	3642	[ETL1]gsasagAfuucAfuuugauaagasusu	3678	usCfsuUfaUfcAfaAfuGfaAfuCfuUfc susu
ETD01745	3643	[ETL1]sgaugAfAfaGfAfuucgGfuaGfuas usu	3679	usAfsuUfaCfcGfaAfuCfuUfuCfaUfc susu
ETD01747	3644	[ETL1]sgaugAfAfaGfdAuUfCfpgUfagu asusu	3680	usAfsuUfaCfcGfaAfuCfuUfuCfaUfc susu
ETD01748	3645	[ETL1]sgaAfGfauucAfuuugAfuAfAfgas usu	3681	usCfsuUfaUfcAfaAfuGfaAfuCfuUfc susu
ETD01750	3646	[ETL1]sgaAfgAfuUfCfdAuUfUfgaUfaa gasusu	3682	usCfsuUfaUfcAfaAfuGfaAfuCfuUfc susu

Table 37B. Example siRNA Base Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01592	3713	GAUGAAAGAUUCGGUAGUA	3749	UACUACCGAAUCUUUCAUC
ETD01594	3714	GAUGAAAGAUUCGGUAGUA	3750	UCUUAUCAAUGAAUCUUC
ETD01745	3715	GAUGAAAGAUUCGGUAGUA	3751	UACUACCGAAUCUUUCAUC
ETD01747	3716	GAUGAAAGAUUCGGUAGUA	3752	UACUACCGAAUCUUUCAUC
ETD01748	3717	GAUGAAAGAUUCGGUAGUA	3753	UCUUAUCAAUGAAUCUUC
ETD01750	3718	UGACAAGUUUUUCACAUCA	3754	UCUUAUCAAUGAAUCUUC

Table 38. Relative mouse *FG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean mouse <i>MTRES1</i> mRNA (Normalized to Group 1, Day 14)
1	3	PBS	0	1.00
2	3	ETD01592	60	0.23
3	3	ETD01594	60	0.35
4	3	ETD01745	60	0.31
5	3	ETD01747	60	0.27
6	3	ETD01748	60	0.42
7	3	ETD01750	60	0.49

Table 39. Relative human *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean human <i>MTRES1</i> mRNA (Normalized to Group 6, Day 14)
1	3	PBS	0	1.00
2	3	ETD01592	60	0.22
3	3	ETD01594	60	0.43
4	3	ETD01745	60	0.49
5	3	ETD01747	60	0.24
6	3	ETD01748	60	0.42
7	3	ETD01750	60	0.51

Table 40. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting *FGG*

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)	
				Day 0	Day 14
1	3	PBS	0	1	0.445
2	3	ETD01592	60	1	0.242
3	3	ETD01594	60	1	0.303

4	3	ETD01745	60	1	0.216
5	3	ETD01747	60	1	0.074
6	3	ETD01748	60	1	1.209
7	3	ETD01750	60	1	0.468

Table 41. PT and APTT Times in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean PT (sec) Day 10	Mean APPT (sec) Day 10
1	3	PBS	0	20.643	81.215
2	3	ETD01592	60	17.058	35.874
3	3	ETD01594	60	14.684	36.348
4	3	ETD01745	60	15.639	33.771
5	3	ETD01747	60	25.907	55.384
6	3	ETD01748	60	15.052	34.784
7	3	ETD01750	60	14.162	34.452

Example 18. Screening of siRNAs targeting human *FGG* mRNA in mice transfected with AAV8-TBG-h-FGG

[00399] Several siRNAs designed to be cross-reactive with human, cynomolgus monkey, rat and mouse *FGG* mRNA were tested for activity in mice following transfection with an adeno-associated viral vector. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in Table 42A, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, “d” is a deoxynucleoside, and “s” is a phosphorothioate linkage.

[00400] Six to eight week old female mice (C57Bl/6) were injected with 10 uL of a recombinant adeno-associated virus 8 (AAV8) vector (2.1 x 10E13 genome copies/mL) by the retroorbital route on Day 14. The recombinant AAV8 contains the open reading frame and a portion of the 5’ and 3’UTRs of the human *FGG* sequence (ENST00000404648) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-FGG). On Day 0, infected mice (n=4) were given a subcutaneous injection of a single 60 ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00401] Mice were euthanized on Day 10 after subcutaneous injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *MTRES1* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for human *FGG* (ThermoFisher, assay# Hs00241038_m1), or mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in

animals receiving PBS. Mice injected with ETD01818, ETD01839, ETD01841, ETD01849, ETD01852, had greatest reductions in mean liver mouse *FGG* mRNA on Day 10 relative to mice receiving PBS. Results are shown in **Table 43**. Mice injected with ETD01818, ETD01839, ETD01841, ETD01849, and ETD01856 had greatest reductions in mean liver human *FGG* mRNA on Day 10 relative to mice receiving PBS. Results are shown in **Table 44**.

[00402] On Day 0 (prior to dosing), 7 and Day 10 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 45**.

[00403] On Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 46**. Mice injected with ETD01818, ETD01839, ETD01840, and ETD01841 had an increase in PT and APPT times on Day 7 and 10 relative to mice receiving PBS.

Table 42A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5'-3') with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5'-3')
ETD01818	3650	[ETL17]sgaugAfAfaGfAfuucgguguasusu	3686	usApscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01839	3652	[ETL17]sgaugAfAfaGfAfuucgguguasusu	3688	usApscuaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01841	3654	[ETL17]sgaugAfAfaGfAfuucgguguasusu	3690	usApscUfacCfgaAfuCfuUfuCfaUfcsusu
ETD01849	3655	[ETL17]sagacaUfCfaUfgaguuggucasusu	3691	usGfsaCfcAfaCfuCfaUfgAfuGfuCfususu
ETD01851	3656	[ETL17]sagacuGfGfAfAfufGfgcagaacasusu	3692	usGfsuUfcUfgCfcAfuUfcCfaGfuCfususu
ETD01852	3657	[ETL17]sugacaagUfUfUfufucacacacacusu	3693	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01853	3658	[ETL17]sugacaagUfUfUfufucacacacacusu	3694	usGfsgAfuGfuGfaAfaAfaCfuUfgUfcsusu
ETD01856	3659	[ETL17]sgacaagUfUfUfufucacacacacacusu	3695	usGfsuAfaGfuGfcCfaCfcUfuGfgUfasusu
ETD01857	3660	[ETL17]sgaguUfUfaUfUfaCfcaaggugasusu	3696	usAfsuUfaAfgUfgCfcAfcCfuUfgGfususu

Table 42B. Example siRNA Base Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01818	3722	UACCAAGGTGGCACUUACA	3758	UACUACCGAAUCUUUCAUC
ETD01839	3724	GAUGAAAGAUUCGGUAGUA	3760	UACUACCGAAUCUUUCAUC
ETD01841	3726	GAAGAUUCAUUUGAUUAGA	3762	UACUACCGAAUCUUUCAUC
ETD01849	3727	GAUGAAAGAUUCGGUAGUA	3763	UGACCAACUCAUGAUGUCU
ETD01851	3728	AGACAUCAUGAGUUGGUCA	3764	UGUUCUGCCAUUCCAGUCU
ETD01852	3729	GACAAGUUUUUCACAUCCA	3765	UGAUGUGAAAAACUUGUCA
ETD01853	3730	UACCAAGGTGGCACUUACA	3766	UGGAUGUGAAAAACUUGUC
ETD01856	3731	ACCAAGGUGGCACUUACUA	3767	UGUAAGUGCCACCUUGGUA
ETD01857	3732	UGACAAGUUUUUCACAUCA	3768	UAGUAAGUGCCACCUUGGU

Table 43. Relative mouse *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean mouse <i>MTRES1</i> mRNA (Normalized to Group 1, Day 10)
1	4	PBS	0	1.00
2	4	ETD01818	60	0.21
3	4	ETD01839	60	0.25
4	4	ETD01841	60	0.21
5	4	ETD01849	60	0.44
6	4	ETD01851	60	0.76

7	4	ETD01852	60	0.53
8	4	ETD01853	60	0.73
9	4	ETD01856	60	0.75
10	4	ETD01857	60	0.83

Table 44. Relative human *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean human <i>MTRES1</i> mRNA (Normalized to Group 6, Day 10)
1	4	PBS	0	N/A
2	4	ETD01818	60	0.43
3	4	ETD01839	60	0.52
4	4	ETD01841	60	0.61
5	4	ETD01849	60	0.26
6	4	ETD01851	60	1.00
7	4	ETD01852	60	0.76
8	4	ETD01853	60	0.72
9	4	ETD01856	60	0.43
10	4	ETD01857	60	0.59

Table 45. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)		
				Day 0	Day 4	Day 10
1	4	PBS	0	1	0.843	0.630
2	4	ETD01818	60	1	0.452	0.367
3	4	ETD01839	60	1	0.516	0.178
4	4	ETD01841	60	1	0.415	0.220
5	4	ETD01849	60	1	0.724	0.619
6	4	ETD01851	60	1	0.498	0.839
7	4	ETD01852	60	1	0.671	0.565
8	4	ETD01853	60	1	2.111	2.185
9	4	ETD01856	60	1	1.436	1.343
10	4	ETD01857	60	1	0.985	0.884

Table 46. PT and APTT Times in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean <i>PT</i> (sec) Day 10	Mean <i>APPT</i> (sec) Day 10
1	4	PBS	0	27.8	53.825
2	4	ETD01818	60	21.975	44.85
3	4	ETD01839	60	38.525	79.275
4	4	ETD01841	60	29.425	71.725
5	4	ETD01849	60	20.6	64.875
6	4	ETD01851	60	20.025	63.375
7	4	ETD01852	60	23.325	82.3
8	4	ETD01853	60	20.475	70.1
9	4	ETD01856	60	21.5	65.2
10	4	ETD01857	60	22.75	66.75

Example 19. Screening of siRNAs targeting human *FGG* mRNA in mice transfected with AAV8-TBG-h-FGG

[00404] Several siRNAs designed to be cross-reactive with human, cynomolgus monkey, rat and mouse *FGG* mRNA were tested for activity in mice following transfection with an adeno-associated viral vector. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in **Table 47A**, where “Nf” is a 2’ fluoro-modified nucleoside, “n” is a 2’ O-methyl modified nucleoside, and “s” is a phosphorothioate linkage.

[00405] Six to eight week old female mice (C57Bl/6) were injected with 10 uL of a recombinant adeno-associated virus 8 (AAV8) vector (2.4 x 10E13 genome copies/mL) by the retroorbital route on Day -14. The recombinant AAV8 contains the open reading frame and a portion of the 5’ and 3’UTRs of the human *FGG* sequence (ENST00000404648) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-FGG). On Day 0, infected mice (n=5) were given a subcutaneous injection of a single 60 ug or 100 ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00406] Mice were euthanized on Day 10 after subcutaneous injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer’s recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer’s instructions. The relative levels of liver *MTRES1* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for human *FGG* (ThermoFisher, assay# Hs00241038_m1), or mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Mice injected with ETD01818, ETD01839, and ETD01841 had substantial reductions in mean liver mouse *FGG* mRNA on Day 10 relative to mice receiving PBS at both 60ug and 100ug doses. Results are shown in **Table 48**. Mice injected with ETD01818, ETD01839, and ETD01841 had substantial reductions in mean liver human *FGG* mRNA on Day 10 relative to mice receiving PBS at both 60ug and 100ug doses. Results are shown in **Table 49**.

[00407] On Day 0 (prior to dosing), 7 and Day 10 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 50**.

[00408] On Day 14 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at IDEXX Laboratories (IDEXX Laboratories, Test# 6005). Results are shown in **Table 51**. Mice injected with ETD01818, ETD01839, and ETD01841 had dose dependent increase in PT and APTT times on Day 7 and 10 relative to mice receiving PBS.

Table 47A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5'-3') with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5'-3')
ETD01818	3650	[ETL17]sgaugAfAfaGfAfuucggguaguasusu	3686	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01839	3652	[ETL17]sgaugAfAfaGfAfuucggguaguasusu	3688	usAfscuaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01841	3654	[ETL17]sgaugAfAfaGfAfuucggguaguasusu	3690	usAfscUfacCfgaAfuCfuUfuCfaUfcsusu

Table 47B. Example siRNA BASE Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01818	3722	UACCAAGGTGGCACUUACA	3758	UACUACCGAAUCUUUCAUC
ETD01839	3724	GAUGAAAGAUUCGGUAGUA	3760	UACUACCGAAUCUUUCAUC
ETD01841	3726	GAAGAUUCAUUUGAUAAGA	3762	UACUACCGAAUCUUUCAUC

Table 48. Relative mouse *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean mouse <i>MTRES1</i> mRNA (Normalized to Group 1, Day 10)
1	5	PBS	0	1.00
2	5	ETD01818	60	0.36
3	5	ETD01818	100	0.19
4	5	ETD01839	60	0.24
5	5	ETD01839	100	0.11
6	5	ETD01841	60	0.17
7	5	ETD01841	100	0.10

Table 49. Relative human *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean human <i>MTRES1</i> mRNA (Normalized to Group 6, Day 10)
1	5	PBS	0	1.00
2	5	ETD01818	60	0.56
3	5	ETD01818	100	0.54
4	5	ETD01839	60	0.49
5	5	ETD01839	100	0.47
6	5	ETD01841	60	0.71
7	5	ETD01841	100	0.61

Table 50. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting *FGG*

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)		
				Day 0	Day 4	Day 10
1	5	PBS	0	1	0.901	0.914
2	5	ETD01818	60	1	0.646	0.373
3	5	ETD01818	100	1	0.520	0.205
4	5	ETD01839	60	1	0.486	0.200
5	5	ETD01839	100	1	0.370	0.090
6	5	ETD01841	60	1	0.402	0.132
7	5	ETD01841	100	1	0.436	0.100

Table 51. PT and APTT Times in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean PT (sec) Day 10	Mean APPT (sec) Day 10
1	5	PBS	0	14.44	40.1
2	5	ETD01818	60	16.9	39.08
3	5	ETD01818	100	21.06	39.64
4	5	ETD01839	60	20.64	50.52
5	5	ETD01839	100	28.68	52.62
6	5	ETD01841	60	19.32	36.18
7	5	ETD01841	100	30.72	61.8

Example 20. Determining the activity of siRNAs targeting FGG in non-human primates

[00409] This study was conducted at Pharmalegacy Laboratories, Inc. on behalf of Empirico. Three groups (n=3/group) of 4-7 year old male cynomolgus monkeys (Zhaoqing Chuangyao Biotechnology Co., Ltd and Guangzhou Xianngguan Biotechnology Co., Ltd) were utilized for this study.

[00410] On Study Day 0, Group 1 cynomolgus monkeys were injected with 2mg/kg ETD01839 (sense strand SEQ ID NO: 3652; antisense strand SEQ ID NO: 3688) at a concentration of 10mg/mL, Group 2 cynomolgus monkeys were injected with 2mg/kg ETD01841 (sense strand SEQ ID NO: 3654; antisense strand SEQ ID NO: 3690) at a concentration of 10mg/mL, Group 3 cynomolgus monkeys were injected with 2mg/kg ETD01926 (sense strand SEQ ID NO: 3675; antisense strand SEQ ID NO: 3711) at a concentration of 10mg/mL. All animals had no abnormal clinical symptoms and well tolerated with single subcutaneous dose at 2 mg/kg of ETD01839, ETD01841 and ETD01926.

[00411] On Study Days -8, -2, 7, 14, 21 and Day 28 body weights were recorded. Results are shown in Table 52.

Table 52. Body Weights in Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	Body Weight (kg)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	5.0	5.3	5.3	5.3	5.2	5.3
	102	Male	4.8	5.6	5.6	5.6	4.7	4.7
	103	Male	4.0	4.3	4.3	4.4	4.1	4.2
G2: ETD01841	201	Male	5.2	5.7	5.7	5.6	5.2	5.3
	202	Male	4.5	5.1	5.1	5.2	4.2	4.3
	203	Male	5.1	5.4	5.4	5.3	5.4	5.3
G3:ETD01926	301	Male	5.9	6.2	6.2	6.1	5.6	5.7
	302	Male	6.5	6.8	6.8	6.8	6.8	6.6
	303	Male	4.0	4.8	4.8	4.7	4.3	4.3

[00412] On Study Day -2 and Day 28, the animals were anesthetized with Zoletil (1.5 – 5.0 mg/kg, i.m.) and xylazine (0.5 – 2.0 mg/kg, i.m.) and 3-4mg liver biopsy was collected. The biopsy was then placed in 10 v/v RNAlater in 20 seconds and stored for 24 hrs at 4°C, the RNAlater™ Stabilization Solution (Thermo Fisher, Catalog# AM7020) was then removed and the liver tissue was stored in freezer until they were shipped to Empirico. There were no abnormal clinical observations for all animals after liver biopsy collection on Day -2 or Day 28. The liver samples were processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments,

catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative level of FGG mRNA in each Study Day 28 liver biopsy sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for cyno FGG (ThermoFisher, assay# Mf02793821_m1) and the cyno housekeeping gene ACTB (ThermoFisher, assay# Mf04354341_g1), and then normalized to the mean value of the Study Day -2 pre-dose liver biopsy using the delta-delta Ct method. Animals treated with ETD01839, ETD01841 or ETD01926 showed decreased liver FGG mRNA levels on Study Day 28 compared to liver biopsies obtained from the same animals on Study Day -2. Results are shown in **Table 53**.

Table 53. Day 28 FGG mRNA liver levels in Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	Relative Liver FGG mRNA Level			
			Day -2	Day -2 Mean	Day 28	Day 28 Mean
G1: ETD01839	101	Male	1.961	1.00	0.533	0.65
	102	Male	0.322		0.812	
	103	Male	1.586		0.649	
G2: ETD01841	201	Male	2.125	1.00	0.38	0.34
	202	Male	0.379		0.383	
	203	Male	1.242		0.274	
G3:ETD01926	301	Male	1.62	1.00	0.265	0.23
	302	Male	3.462		0.214	
	303	Male	0.178		0.21	

[00413] On Study Days -2, -8, 7, 14, 21, and Day 28 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for PT and APTT at Pharmalegacy Laboratories, Inc. and the remaining plasma samples were stored in a freezer until they were shipped to Empirico. Plasma sample were then transferred to IDEXX Laboratories and plasma fibrinogen levels were measured by the Clauss method (IDEXX Laboratories, Test# 6308). Results are shown in **Table 54-55**. Animals treated with ETD01839, ETD01841 or ETD01926 showed a decrease in plasma fibrinogen starting on Study Day 7 though Study Day 28 when compared to Study Day -8 and Study Day -2, prior to treatment. Results are shown in **Table 56**.

Table 54. Prothrombin time in Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	PT (sec)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	9.6	9.8	10.1	11.9	11.6	11.6
	102	Male	10.3	10.2	10.3	11.3	10.2	11.7
	103	Male	9.7	10.3	9.8	10.9	11	10.7
G2: ETD01841	201	Male	9.3	9.9	10.5	12.3	12	12.4
	202	Male	9.2	9.9	10.4	11.9	12	11.8
	203	Male	9.7	9.5	9.3	9.9	6.6	10.2

G3:ETD0192 6	301	Male	9.5	10	9.7	10.6	10.7	11.1
	302	Male	9.1	10	10.2	11.1	11.3	11.9
	303	Male	9.8	10.6	10.3	11.3	11.6	11.4

Table 55. Activated Partial Thromboplastin time in Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	APTT (sec)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	18.7	20.5	19.6	19.2	19.2	17.8
	102	Male	19.4	20.2	19.7	20.1	19.8	17.9
	103	Male	18.7	20.8	19.5	19.4	20.1	18.6
G2: ETD01841	201	Male	18.5	18.8	18.9	18.4	19.5	17.7
	202	Male	18.4	20.5	18.4	17.8	18.6	17.4
	203	Male	22.5	20.6	19.2	18.6	19.2	18.7
G3:ETD0192 6	301	Male	19.3	20.6	19.4	20.1	19.7	18.5
	302	Male	15.5	18.2	16.8	16.9	16.6	15.5
	303	Male	21.7	22.4	22.4	23.4	21.2	20.6

Table 56. Plasma fibrinogen levels in Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	Fibrinogen Plasma Level (Clauss method, mg/dL)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	N/A	373	253	148	151	81
	102	Male	478	391	259	124	222	203
	103	Male	343	419	248	188	80	208
G2: ETD01841	201	Male	277	316	180	117	155	120
	202	Male	581	272	169	126	148	125
	203	Male	674	519	286	295	82	318
G3:ETD0192 6	301	Male	598	418	464	234	234	227
	302	Male	663	390	479	154	140	129
	303	Male	339	311	241	188	174	158

[00414] On Study Days -8, -2, 7, 14, 21, and Day 28 blood was collected into tubes with no anti-coagulant and serum collected. Clinical chemistry parameters containing ALT, AST, ALP, DBIL, TBIL, GLU, UREA, CREA, TP and CGT were analyzed at Pharmalegacy Laboratories, Inc.

[00415] Results are shown in Table 57-66.

Table 57. Clinical Chemistry ALT results of Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	ALT (U/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	60	43	52	50	67	41
	102	Male	40	29	28	32	33	49
	103	Male	55	42	46	39	41	40
G2: ETD01841	201	Male	68	63	59	51	59	35
	202	Male	159	88	81	55	52	48
	203	Male	55	39	46	39	37	64
G3:ETD0192 6	301	Male	66	42	41	40	40	43
	302	Male	71	55	106	70	57	25
	303	Male	44	40	59	52	43	59

Table 58. Clinical Chemistry AST results of Cynomolgus Monkeys treated with siRNAs targeting FG

Treatment group	Animal No.	Gender	AST (U/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	61	48	48	55	99	43
	102	Male	32	35	35	33	41	41
	103	Male	50	62	61	53	69	43
G2: ETD01841	201	Male	51	54	56	52	53	30
	202	Male	54	56	54	44	51	49
	203	Male	36	32	34	31	39	48
G3:ETD01926	301	Male	44	51	43	46	43	56
	302	Male	38	62	50	46	44	30
	303	Male	32	33	41	37	38	61

Table 59. Clinical Chemistry ALP results of Cynomolgus Monkeys treated with siRNAs targeting FG

Treatment group	Animal No.	Gender	ALP(U/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	580	593	597	612	664	586
	102	Male	292	326	318	292	335	457
	103	Male	389	390	397	349	406	687
G2: ETD01841	201	Male	590	667	591	572	610	289
	202	Male	509	523	533	553	535	619
	203	Male	263	288	308	266	289	618
G3:ETD01926	301	Male	678	692	663	606	659	373
	302	Male	431	469	895	652	490	271
	303	Male	481	495	543	546	569	636

Table 60. Clinical Chemistry DBIL results of Cynomolgus Monkeys treated with siRNAs targeting FG

Treatment group	Animal No.	Gender	DBIL (μmol/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	0.4	0.4	0.7	0.7	1.1	0.6
	102	Male	0.4	0.4	0.7	0.7	0.8	0.5
	103	Male	0.9	0.5	0.7	0.7	0.7	0.7
G2: ETD01841	201	Male	0.2	0.8	1.1	0.8	0.7	0.8
	202	Male	0.5	0.6	0.7	0.8	0.6	0.6
	203	Male	0.4	0.5	0.9	0.7	0.8	0.8
G3:ETD01926	301	Male	0.6	0.7	0.7	0.7	0.8	0.4
	302	Male	0.5	0.8	1.1	0.5	0.9	0.7
	303	Male	0.4	0.5	1.2	1.3	1	0.8

Table 61. Clinical Chemistry TBIL results of Cynomolgus Monkeys treated with siRNAs targeting FG

Treatment group	Animal No.	Gender	TBIL (μmol/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	1	0.3	1.1	1.3	1.6	1.6
	102	Male	0.2	0	1	1.1	1.5	1.5
	103	Male	0.3	0.1	0.7	1.2	0.8	1.4

G2: ETD01841	201	Male	0.8	1	1.6	1.5	1.3	1.4
	202	Male	1.2	0.7	0.9	1.2	0.8	0.9
	203	Male	0.1	0.5	1	0.8	1.1	2.1
G3:ETD0192 6	301	Male	0.8	0.4	0.7	1.4	0.9	0.8
	302	Male	0.6	1.5	1.9	1.9	1.2	1.5
	303	Male	0.1	1.1	1.9	2.2	1.7	2.3

**Table 62. Clinical Chemistry GLU results of Cynomolgus Monkeys treated with siRNAs targeting
FGG**

Treatment group	Animal No.	Gender	GLU (mmol/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	5.8	3.1	5.7	5.2	2.3	5.5
	102	Male	5.1	3.4	4.3	4.3	2.7	3.8
	103	Male	4	2.6	3.8	3.1	2.9	3.1
G2: ETD01841	201	Male	4.2	3.1	5.7	4.6	3.8	3.8
	202	Male	7.3	4.1	5.4	4.3	3.8	4.7
	203	Male	3.7	2.7	4.5	3.2	2.6	5.3
G3:ETD0192 6	301	Male	5.5	2.8	2.8	3.2	3.3	3.2
	302	Male	4.5	2.5	4	3.2	3.3	5
	303	Male	5.1	3.6	4.1	3.8	3.3	4.1

**Table 63. Clinical Chemistry UREA results of Cynomolgus Monkeys treated with siRNAs targeting
FGG**

Treatment group	Animal No.	Gender	UREA (mmol/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	6.04	4.93	5.19	6.38	6.62	6.15
	102	Male	6.26	5.58	5.73	5.54	6.36	6.57
	103	Male	7.32	6.82	8.03	7.17	7.21	8.39
G2: ETD01841	201	Male	6.12	7.14	6.39	6.6	6.33	7.84
	202	Male	5.87	5.48	6.46	5.87	6.2	5.75
	203	Male	8.72	7.07	8.37	8.59	9.2	6.22
G3:ETD0192 6	301	Male	8.18	7.28	8.57	8.59	7.53	6.62
	302	Male	5.8	6.1	6.15	6.6	7.05	5.77
	303	Male	6.17	5.69	6.53	7.07	5.98	6.86

**Table 64. Clinical Chemistry CREA results of Cynomolgus Monkeys treated with siRNAs targeting
FGG**

Treatment group	Animal No.	Gender	CREA (μmol/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	56	52	58	57	59	65
	102	Male	63	62	66	67	62	92
	103	Male	69	68	69	67	67	79
G2: ETD01841	201	Male	63	60	60	61	60	76
	202	Male	66	60	62	65	63	65
	203	Male	73	67	82	75	77	60
G3:ETD0192 6	301	Male	72	71	83	77	70	66
	302	Male	93	89	87	87	86	66
	303	Male	61	56	63	60	58	57

Table 65. Clinical Chemistry TP results of Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	TP (g/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	76.9	73.3	79	71	70.3	75.1
	102	Male	66.8	68.3	68.1	63.9	68.1	81.3
	103	Male	80.3	78.2	79.2	69.5	77.5	76.5
G2: ETD01841	201	Male	74	78.3	75.6	67.8	73.3	73.8
	202	Male	77.9	80.5	82.1	80.1	75.2	84.7
	203	Male	72.3	73.4	78.9	69.8	70.4	74.8
G3:ETD01926	301	Male	71.6	75.1	77.4	70.2	68.5	76.9
	302	Male	79.9	76.5	83.9	81.3	75	71
	303	Male	71.1	70.7	74.3	71.8	70.1	75

Table 66. Clinical Chemistry CGT results of Cynomolgus Monkeys treated with siRNAs targeting FGG

Treatment group	Animal No.	Gender	CGT (U/L)					
			-8	-2	7	14	21	28
G1: ETD01839	101	Male	81	77	81	81	80	70
	102	Male	83	81	97	90	100	88
	103	Male	111	111	104	97	109	118
G2: ETD01841	201	Male	86	94	89	85	89	59
	202	Male	123	127	117	123	117	139
	203	Male	51	55	59	51	50	90
G3:ETD01926	301	Male	109	115	107	103	106	107
	302	Male	60	56	135	112	93	94
	303	Male	59	61	65	64	65	79

Example 21. Discovery toxicity siRNAs targeting human, cynomolgus monkey, rat and mouse FGG in mice

[00416] Several siRNAs designed to be cross-reactive with human, cynomolgus monkey and mouse *FGG* mRNA were tested for toxicity in mice. The siRNAs were attached to the GalNAc ligand ETL17. The siRNA sequences are shown in **Table 66A**, where Nf is a 2' fluoro-modified nucleoside, n is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00417] Six to eight week old female mice (strain ICR, n=4) were given a subcutaneous injection on Day 0, 7, and Day 14 of a 200ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00418] Mice were euthanized on Day 14 after injection and a liver sample from each was collected and placed in RNeasy lysis buffer (Qiagen) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver *FGG* mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro

Real-Time PCR System using TaqMan assays for mouse *FGG* (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene *PPIA* (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean *FGG* mRNA level in animals receiving PBS. Results are shown in **Table 67**

[00419] On Day 0 (prior to dosing) and Day 21 blood was collected into tubes with 0.2mL sodium citrate for collection of plasma. Plasma samples were analyzed for fibrinogen levels by ELISA (Molecular Innovations Mouse Fibrinogen Antigen ELISA kit, Cat# MFBGNKT). Results are shown in **Table 68**.

[00420] On Day 2, 9, and Day 21 blood was collected into tubes with no anti-coagulant abd serum collected. Clinical chemistry parameters containing ALT, AST, ALP, TBIL, GLU, BUN, and CREAT were analyzed at IDEXX Laboratories (IDEXX Laboratories, Test# 62849). Results are shown in **Table 69-74**.

Table 66A. Example siRNA Sequences

ETD#	SEQ ID NO	Sense Strand Sequence (5'-3') with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5'-3')
ETD01818	3641	[ETL1]gsasugAfAfaGfAfuucgguaguasusu	3677	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01839	3642	[ETL1]gsasagAfuucAfuugauaagasusu	3678	usAfscuaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01841	3643	[ETL1]sgaugAfAfaGfAfuucgGfuaGfuasusu	3679	usAfscUfacCfgaAfuCfuUfuCfaUfcsusu
ETD01852	3644	[ETL1]sgaugAfAfaGfdAuUfCfggUfaguasusu	3680	usGfsaUfgUfgAfaAfaAfcUfuGfuCfasusu
ETD01926	3645	[ETL1]sgaAfGfauucAfuugAfuAfAfgasusu	3681	usGfsaUfguGfaaaaAfcUfuGfuCfasusu

Table 66B. Example siRNA BASE Sequences

siRNA Name	SEQ ID NO:	Sense Strand Base Sequence (5' to 3'), without 3' overhangs	SEQ ID NO:	Antisense Strand Base Sequence (5' to 3'), without 3' overhangs
ETD01818	3641	GAUGAAAGAUUCGGUAGUA UU	3677	UACUACCGAAUCUUUCAUC UU
ETD01839	3642	GAUGAAAGAUUCGGUAGUA UU	3678	UACUACCGAAUCUUUCAUC UU
ETD01841	3643	GAUGAAAGAUUCGGUAGUA UU	3679	UACUACCGAAUCUUUCAUC UU
ETD01852	3644	UGACAAGUUUUUCACAUCA UU	3680	UGAUGUGAAAAACUUGUCA UU
ETD01926	3645	UGACAAGUUUUUCACAUCA UU	3681	UGAUGUGAAAAACUUGUCA UU

Table 67. Relative *FGG* mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean <i>FGG</i> mRNA (Normalized to Group 1, Day 14)
1	4	PBS	0	1.00
2	4	ETD01818	200ugx3	0.10
3	4	ETD01839	200ugx3	0.04
4	4	ETD01841	200ugx3	0.05
5	4	ETD01852	200ugx3	0.10
6	4	ETD01926	200ugx3	0.05

Table 68. Fibrinogen Levels in Plasma of Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean Fibrinogen (Normalized, Day 0)	
				Day 0	Day 7
1	4	PBS	0	1.00	0.63
2	4	ETD01818	200ugx3	1.00	0.03
3	4	ETD01839	200ugx3	1.00	0.01
4	4	ETD01841	200ugx3	1.00	0.01
5	4	ETD01852	200ugx3	1.00	0.15
6	4	ETD01926	200ugx3	1.00	0.14

Table 69. Clinical Chemistry ALT in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean ALT (U/L)		
				Day 2	Day 9	Day 21
1	4	PBS	0	23.25	24	27
2	4	ETD01818	200ugx3	93.25	23	22.5
3	4	ETD01839	200ugx3	85	30.75	27
4	4	ETD01841	200ugx3	24.75	24	26.75
5	4	ETD01852	200ugx3	24.25	33	30
6	4	ETD01926	200ugx3	25.5	26.75	26.75

Table 70. Clinical Chemistry AST in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean AST (U/L)		
				Day 2	Day 9	Day 21
1	4	PBS	0	60.5	53	64
2	4	ETD01818	200ugx3	126	54.25	49.5
3	4	ETD01839	200ugx3	122.25	56.75	55
4	4	ETD01841	200ugx3	55.25	53	64
5	4	ETD01852	200ugx3	56.25	60.75	59.25
6	4	ETD01926	200ugx3	59.25	62.25	62

Table 71. Clinical Chemistry ALP in Mice treated with siRNAs targeting FGG

Group	n	Treatment	Dose (ug)	Mean ALP (U/L)		
				Day 2	Day 9	Day 21
1	4	PBS	0	129.75	118.5	94.25
2	4	ETD01818	200ugx3	123.75	107	84
3	4	ETD01839	200ugx3	115.5	96.75	109.75
4	4	ETD01841	200ugx3	95.25	81	82
5	4	ETD01852	200ugx3	120.25	118	101.25
6	4	ETD01926	200ugx3	140.75	126.25	110.25

Table 72. Clinical Chemistry TBILI in Mice treated with siRNAs targeting FG

Group	n	Treatment	Dose (ug)	Mean TBILI (mg/dL)		
				Day 2	Day 9	Day 21
1	4	PBS	0	0.175	0.2	0.2
2	4	ETD01818	200ugx3	0.125	0.15	0.1
3	4	ETD01839	200ugx3	0.15	0.2	0.125
4	4	ETD01841	200ugx3	0.15	0.2	0.125
5	4	ETD01852	200ugx3	0.1	0.15	0.15
6	4	ETD01926	200ugx3	0.125	0.2	0.175

Table 73. Clinical Chemistry BUN in Mice treated with siRNAs targeting FG

Group	n	Treatment	Dose (ug)	Mean BUN (mg/dL)		
				Day 2	Day 9	Day 21
1	4	PBS	0	25	25.5	23.5
2	4	ETD01818	200ugx3	24.25	25	21
3	4	ETD01839	200ugx3	22.5	26.5	20.25
4	4	ETD01841	200ugx3	25.75	24.5	24
5	4	ETD01852	200ugx3	26	25.75	23.75
6	4	ETD01926	200ugx3	24	22	23

Table 74. Clinical Chemistry BUN in Mice treated with siRNAs targeting FG

Group	n	Treatment	Dose (ug)	Mean CREAT (mg/dL)		
				Day 2	Day 9	Day 21
1	4	PBS	0	0.075	0	0.075
2	4	ETD01818	200ugx3	0.1	0.025	0.025
3	4	ETD01839	200ugx3	0.1	0.05	0.075
4	4	ETD01841	200ugx3	0.175	0.025	0.05
5	4	ETD01852	200ugx3	0.1	0.025	0.075
6	4	ETD01926	200ugx3	0.1	0	0.075

Example 22: Determining the activity of species cross-reactive siRNAs targeting FG in mice

[00421] 3 groups (n=4/group) of 8-week-old male ICR mice (Invigo) were utilized in this study. On Study Day 0, Group 1 mice were injected subcutaneously with 100 uL of sterile PBS, Group 2 mice were subcutaneously injected with 60 ug of ETD01811 in 100 uL of sterile PBS, and Group 3 mice were subcutaneously injected with 200 ug ETD01818 in 100 uL of sterile PBS. On Study Day 14, the animals from all Groups were anesthetized and then euthanized. A liver sample was collected from all animals and placed in RNeasy Lysis Solution (Qiagen, Catalog# 69903). The liver samples were processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the

manufacturer's recommendations. The relative level of FGG mRNA in each liver sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for mouse FGG (ThermoFisher, assay# Mm00513575_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1), and then normalized to the mean value of the control mice (Group 1) using the delta-delta Ct method.

[00422] The results of the liver mRNA analyses are shown in **Table 75** below. Animals treated with ETL1-targeted siRNA (ETD01811, Group 2) had 78% relative knockdown while ETL17-targeted siRNA (ETD01818, Group 3) had 83% knockdown of liver FGG mRNA levels compared with mice injected with PBS (Group 1).

Table 75: Day 14 FGG mRNA liver levels in mice treated with siRNAs targeting FGG

Group #	Treatment	Mean
1	PBS	1.00
2	ETD01811	0.22
3	ETD01818	0.17

Example 23: Oligonucleotide Synthesis

[00423] Oligonucleotides such as siRNAs may be synthesized according to phosphoramidite technology on a solid phase. For example, a K&A oligonucleotide synthesizer may be used. Syntheses may be performed on a solid support made of controlled pore glass (CPG, 500 Å or 600 Å, obtained from AM Chemicals, Oceanside, CA, USA). All 2'-Ome and 2'-F phosphoramidites may be purchased from Hongene Biotech (Union City, CA, USA). All phosphoramidites may be dissolved in anhydrous acetonitrile (100 mM) and molecular sieves (3 Å) may be added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) may be used as activator solution. Coupling times may be 9-18 min (e.g. with a GalNAc such as ETL17), 6 min (e.g. with 2'Ome and 2'F). In order to introduce phosphorothioate linkages, a 100 mM solution of 3-phenyl 1,2,4-dithiazoline-5-one (POS, obtained from PolyOrg, Inc., Leominster, Mass., USA) in anhydrous acetonitrile may be employed.

[00424] After solid phase synthesis, the dried solid support may be treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution (Aldrich) for two hours at 30° C. The solution may be evaporated and the solid residue may be reconstituted in water and purified by anionic exchange HPLC using a TKSgel SuperQ-5PW 13u column. Buffer A may be 20 mM Tris, 5 mM EDTA, pH 9.0 and contained 20% Acetonitrile and buffer B may be the same as buffer A with the addition of 1 M sodium chloride. UV traces at 260 nm may be recorded. Appropriate fractions may be pooled then desalted using Sephadex G-25 medium.

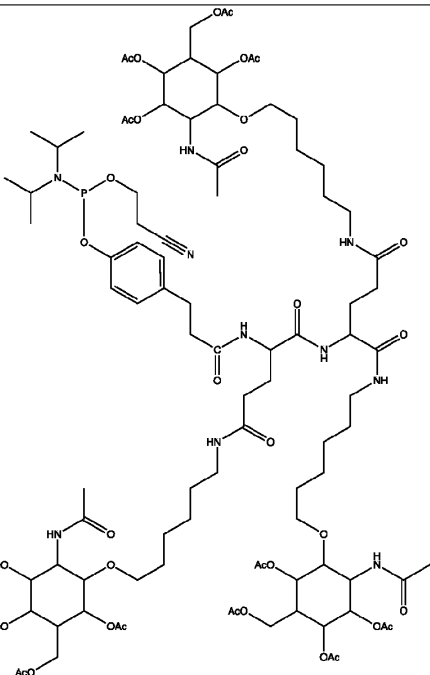
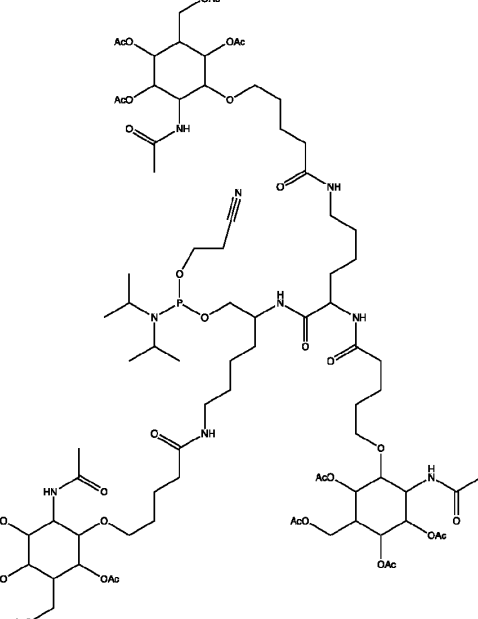
[00425] Equimolar amounts of sense and antisense strand may be combined to prepare a duplex. The duplex solution may be prepared in 0.1×PBS (Phosphate-Buffered Saline, 1×, Gibco). The duplex solution may be annealed at 95° C. for 5 min, and cooled to room temperature slowly. Duplex concentration may be determined by measuring the solution absorbance on a UV-Vis spectrometer at 260 nm in 0.1×PBS. For some experiments, a conversion factor may be calculated from an experimentally determined extinction coefficient.

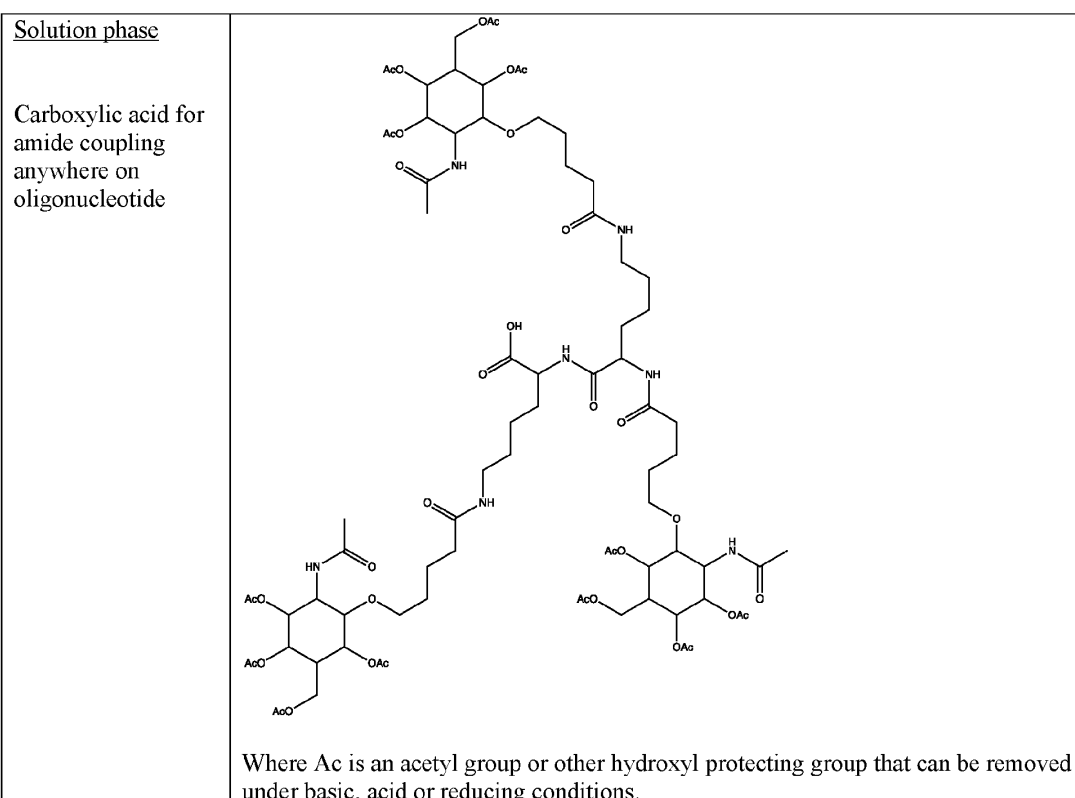
Example 24: GalNAc ligand for hepatocyte targeting of oligonucleotides

[00426] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. Reagents for GalNAc conjugation to oligonucleotides are shown in **Table 76**.

Table 76. GalNAc Conjugation Reagents

Type of conjugation	Structure
<u>Solid phase 3' attachment</u> where squiggly line is rest of oligonucleotide chain and right-most OH is where attachment to solid phase is.	

<u>Solid phase 5'</u> <u>attachment</u> phosphoramidite	
<u>Solid phase 5'</u> <u>attachment</u> Phosphoramidite	



[00427] In solution phase conjugation, the oligonucleotide sequence—including a reactive conjugation site—is formed on the resin. The oligonucleotide is then removed from the resin and GalNAc is conjugated to the reactive site.

[00428] The carboxy GalNAc derivatives may be coupled to amino-modified oligonucleotides. The peptide coupling conditions are known to the skilled in the art using a carbodiimide coupling agent like DCC (N,N'-Dicyclohexylcarbodiimide), EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide) or EDC.HCl (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) and an additive like HOBt (1-hydroxybenzotriazole), HOSu (N-hydroxysuccinimide), TBTU (N,N,N',N'-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or HOAt (1-Hydroxy-7-azabenzotriazole) and common combinations thereof such as TBTU/HOBt or HBTU/HOAt to form activated amine-reactive esters.

[00429] Amine groups may be incorporated into oligonucleotides using a number of known, commercially available reagents at the 5' terminus, 3' terminus or anywhere in between.

[00430] Non-limiting examples of reagents for oligonucleotide synthesis to incorporate an amino group include:

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

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

[00431] Internal (base modified):

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

[00432] Solution phase conjugations may occur after oligonucleotide synthesis via reactions between non-nucleosidic nucleophilic functional groups that are attached to the oligonucleotide and electrophilic GalNAc reagents. Examples of nucleophilic groups include amines and thiols, and examples of electrophilic reagents include activated esters (e.g. N-hydroxysuccinimide, pentafluorophenyl) and maleimides.

Example 25: GalNAc ligands for hepatocyte targeting of oligonucleotides

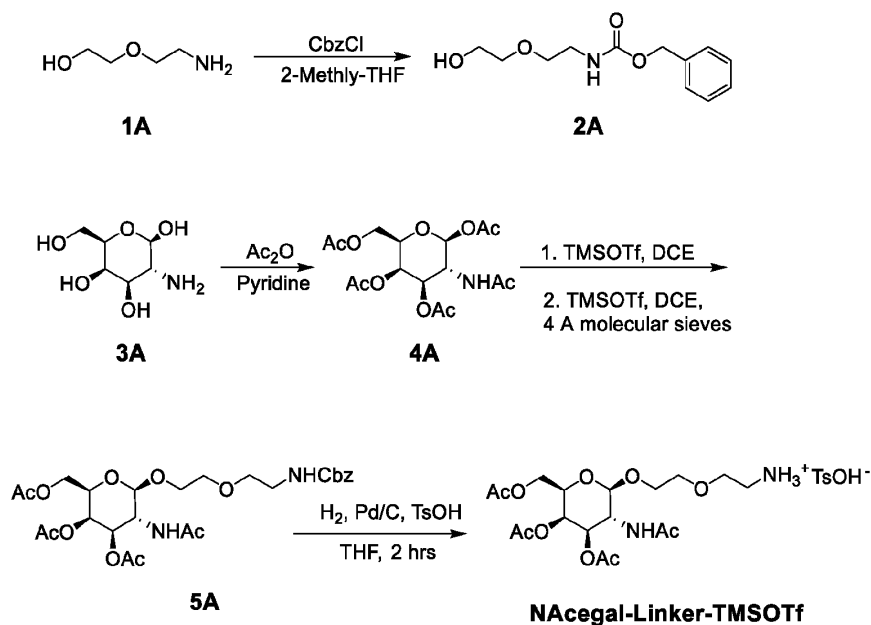
[00433] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. A non-limiting example of a phosphoramidite reagent for GalNAc conjugation to a 5' end oligonucleotide is shown in **Table 77**.

Table 77. GalNAc Conjugation Reagent

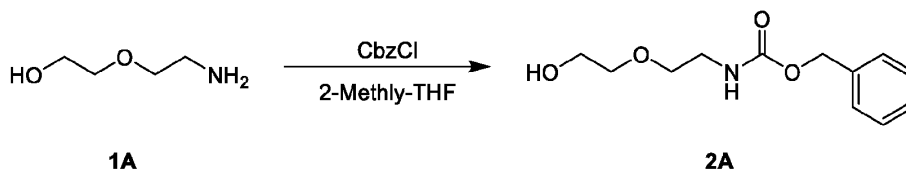
Type of conjugation	Structure
<u>Solid phase 5' attachment</u> phosphoramidite	

[00434] The following includes examples of synthesis reactions used to create a GalNAc moiety:

Scheme for the preparation of Nacegal-Linker-TMSOTf

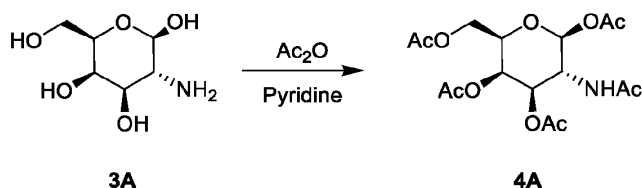


General procedure for preparation of Compound 2A



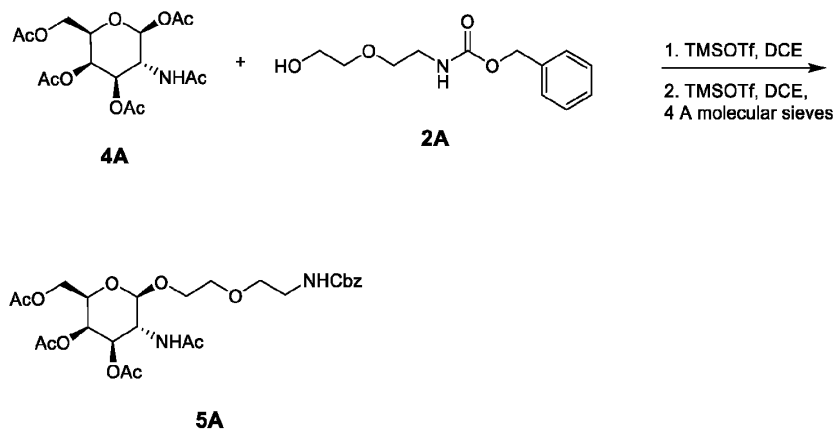
[00435] To a solution of Compound 1A (500 g, 4.76 mol, 476 mL) in 2-Methyl-THF (2.00 L) is added CbzCl (406 g, 2.38 mol, 338 mL) in 2-Methyl-THF (750 mL) dropwise at 0 °C. The mixture is stirred at 25 °C for 2 hrs under N₂ atmosphere. TLC (DCM: MeOH = 20:1, PMA) may indicate CbzCl is consumed completely and one new spot (R_f = 0.43) formed. The reaction mixture is added HCl/EtOAc (1 N, 180 mL) and stirred for 30 mins, white solid is removed by filtration through celite, the filtrate is concentrated under vacuum to give Compound 2A (540 g, 2.26 mol, 47.5% yield) as a pale yellow oil and used into the next step without further purification. ¹H NMR: δ 7.28 – 7.41 (m, 5 H), 5.55 (br s, 1 H), 5.01 – 5.22 (m, 2 H), 3.63 – 3.80 (m, 2 H), 3.46 – 3.59 (m, 4 H), 3.29 – 3.44 (m, 2 H), 2.83 – 3.02 (m, 1 H).

General procedure for preparation of Compound 4A



[00436] To a solution of Compound 3A (1.00 kg, 4.64 mol, HCl) in pyridine (5.00 L) is added acetyl acetate (4.73 kg, 46.4 mol, 4.34 L) dropwise at 0 °C under N₂ atmosphere. The mixture is stirred at 25 °C for 16 hrs under N₂ atmosphere. TLC (DCM: MeOH = 20:1, PMA) indicated Compound 3A is consumed completely and two new spots (R_f = 0.35) formed. The reaction mixture is added to cold water (30.0 L) and stirred at 0 °C for 0.5 hr, white solid formed, filtered and dried to give Compound 4A (1.55 kg, 3.98 mol, 85.8% yield) as a white solid and used in the next step without further purification. ¹H NMR: δ 7.90 (d, J = 9.29 Hz, 1 H), 5.64 (d, J = 8.78 Hz, 1 H), 5.26 (d, J = 3.01 Hz, 1 H), 5.06 (dd, J = 11.29, 3.26 Hz, 1 H), 4.22 (t, J = 6.15 Hz, 1 H), 3.95 – 4.16 (m, 3 H), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.90 (s, 3 H), 1.78 (s, 3 H).

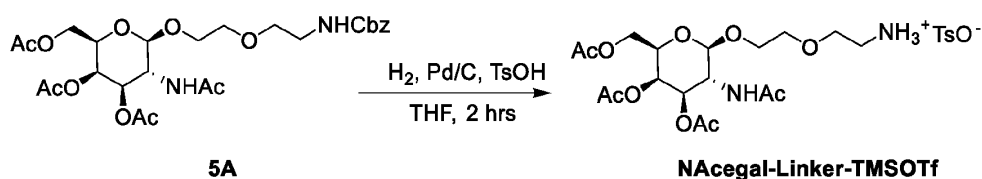
General procedure for preparation of Compound 5A



[00437] To a solution of Compound 4A (300 g, 771 mmol) in DCE (1.50 L) is added TMSOTf (257 g, 1.16 mol, 209 mL) and stirred for 2 hrs at 60 °C, and then stirred for 1 hr at 25 °C. Compound 2A (203 g, 848 mmol) is dissolved in DCE (1.50 L) and added 4 Å powder molecular sieves (150 g) stirring for 30 mins under N₂ atmosphere. Then the solution of Compound 4A in DCE is added dropwise to the mixture

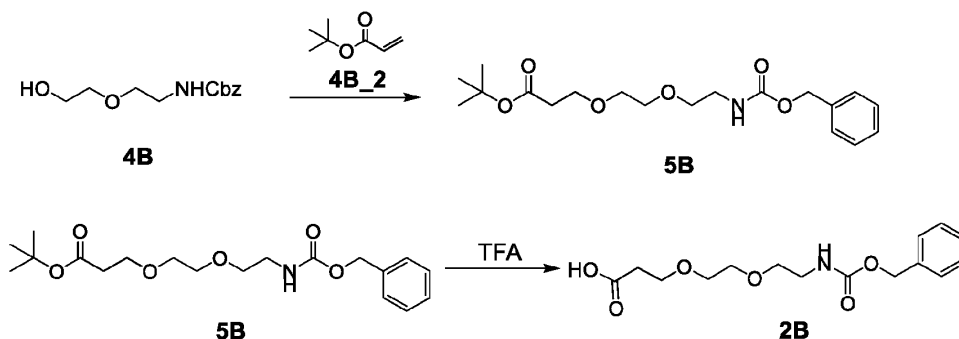
at 0 °C. The mixture is stirred at 25 °C for 16 hrs under N₂ atmosphere. TLC (DCM: MeOH = 25:1, PMA) indicated Compound 4A is consumed completely and new spot ($R_f = 0.24$) formed. The reaction mixture is filtered and washed with sat. NaHCO₃ (2.00 L), water (2.00 L) and sat. brine (2.00 L). The organic layer is dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is triturated with 2-Me-THE/heptane (5/3, v/v, 1.80 L) for 2 hrs, filtered and dried to give Compound 5A (225 g, 389 mmol, 50.3% yield, 98.4% purity) as a white solid. ¹H NMR: δ 7.81 (d, $J = 9.29$ Hz, 1 H), 7.20 – 7.42 (m, 6 H), 5.21 (d, $J = 3.26$ Hz, 1 H), 4.92 – 5.05 (m, 3 H), 4.55 (d, $J = 8.28$ Hz, 1 H), 3.98 – 4.07 (m, 3 H), 3.82 – 3.93 (m, 1 H), 3.71 – 3.81 (m, 1 H), 3.55 – 3.62 (m, 1 H), 3.43 – 3.53 (m, 2 H), 3.37 – 3.43 (m, 2 H), 3.14 (q, $J = 5.77$ Hz, 2 H), 2.10 (s, 3 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 1.77 (s, 3 H).

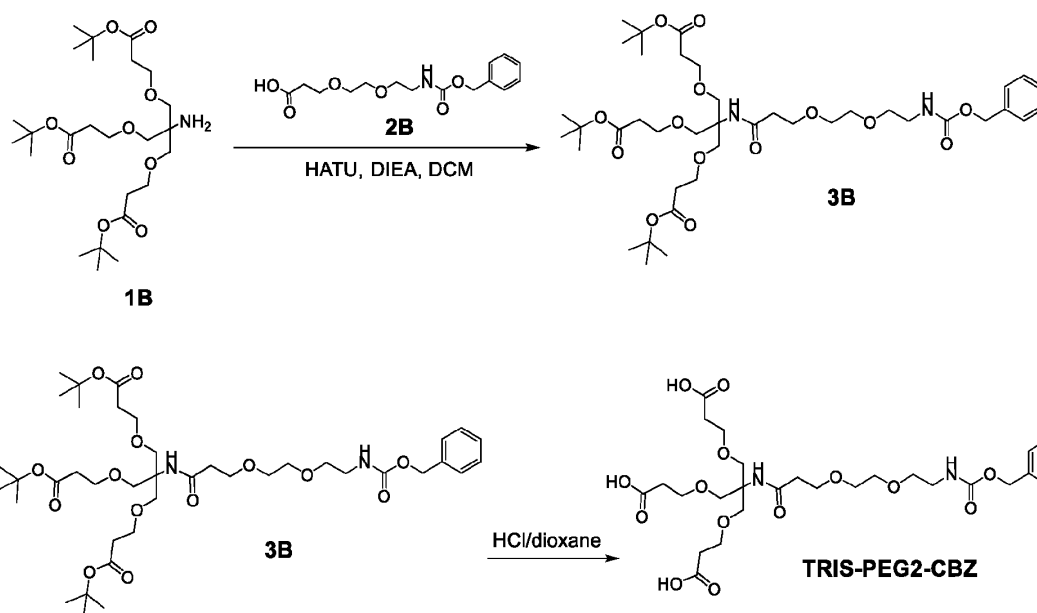
General procedure for preparation of Nacegal-Linker-Tosylate salt



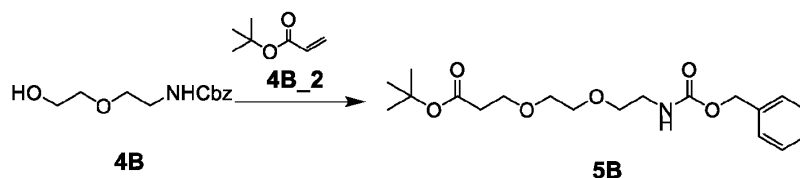
[00438] To a solution of Compound 5A (200 g, 352 mmol) in THF (1.0 L) is added dry Pd/C (15.0 g, 10% purity) and TsOH (60.6 g, 352 mmol) under N₂ atmosphere. The suspension is degassed under vacuum and purged with H₂ several times. The mixture is stirred at 25 °C for 3 hrs under H₂ (45 psi) atmosphere. TLC (DCM: MeOH = 10:1, PMA) indicated Compound 5A is consumed completely and one new spot ($R_f = 0.04$) is formed. The reaction mixture is filtered and concentrated (≤ 40 °C) under reduced pressure to give a residue. Diluted with anhydrous DCM (500 mL, dried overnight with 4 Å molecular sieves (dried at 300 °C for 12 hrs)) and concentrate to give a residue and run Karl Fisher (KF) to check for water content. This is repeated 3 times with anhydrous DCM (500 mL) dilutions and concentration to give Nacegal-Linker-TMSOTf (205 g, 95.8% yield, TsOH salt) as a foamy white solid. ¹H NMR: δ 7.91 (d, $J = 9.03$ Hz, 1 H), 7.53 – 7.86 (m, 2 H), 7.49 (d, $J = 8.03$ Hz, 2 H), 7.13 (d, $J = 8.03$ Hz, 2 H), 5.22 (d, $J = 3.26$ Hz, 1 H), 4.98 (dd, $J = 11.29, 3.26$ Hz, 1 H), 4.57 (d, $J = 8.53$ Hz, 1 H), 3.99 – 4.05 (m, 3 H), 3.87 – 3.94 (m, 1 H), 3.79 – 3.85 (m, 1 H), 3.51 – 3.62 (m, 5 H), 2.96 (br t, $J = 5.14$ Hz, 2 H), 2.29 (s, 3 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.89 (s, 3 H), 1.78 (s, 3 H).

Scheme for the preparation of TRIS-PEG2-CBZ



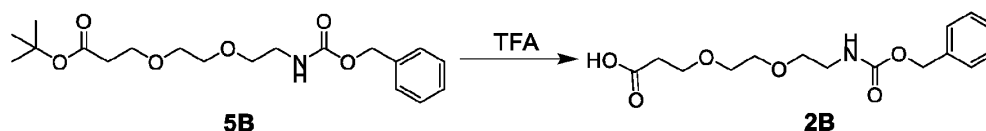


General procedure for preparation of Compound 5B



[00439] To a solution of Compound 4B (400 g, 1.67 mol, 1.00 *eq*) and NaOH (10 M, 16.7 mL, 0.10 *eq*) in THF (2.00 L) is added Compound 4B₂ (1.07 kg, 8.36 mol, 1.20 L, 5.00 *eq*), the mixture is stirred at 30 °C for 2 hrs. LCMS showed the desired MS is given. Five batches of solution are combined to one batch, then the mixture is diluted with water (6.00 L), extracted with ethyl acetate (3.00 L*3), the combined organic layer is washed with brine (3.00 L), dried over Na₂SO₄, filtered and concentrated under vacuum. The crude is purified by column chromatography (SiO₂, petroleum ether : ethyl acetate=100:1-10:1, R_f=0.5) to give Compound 5B (2.36 kg, 6.43 mol, 76.9% yield) as light yellow oil. HNMR: δ 7.31-7.36 (m, 5 H), 5.38 (s, 1 H), 5.11-5.16 (m, 2 H), 3.75 (t, J=6.4 Hz), 3.54-3.62 (m, 6 H), 3.39 (d, J=5.2 Hz), 2.61 (t, J=6.0 Hz).

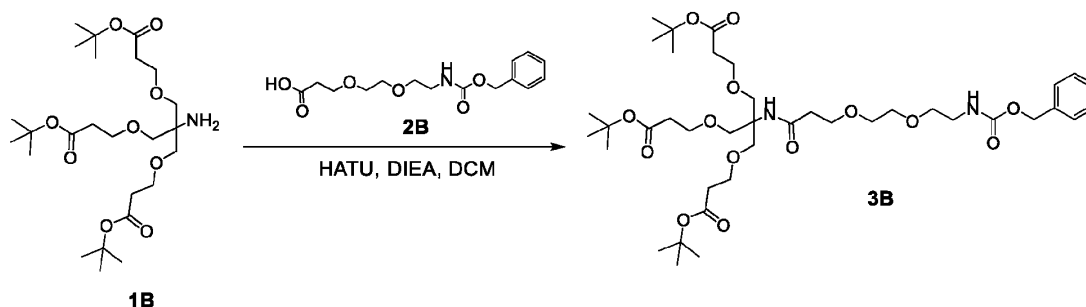
General procedure for preparation of 3-oxo-1-phenyl-2,7,10-trioxa-4-azatridecan-13-oic acid (Compound 2B below)



[00440] To a solution of Compound 5B (741 g, 2.02 mol, 1.00 *eq*) in DCM (2.80 L) is added TFA (1.43 kg, 12.5 mol, 928 mL, 6.22 *eq*), the mixture is stirred at 25 °C for 3 hrs. LCMS showed the desired MS is given. The mixture is diluted with DCM (5.00 L), washed with water (3.00 L*3), brine (2.00 L), the combined organic layer is dried over Na₂SO₄, filtered and concentrated under vacuum to give

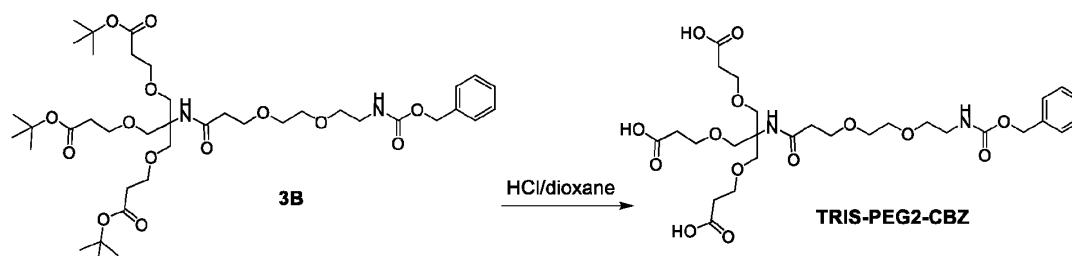
Compound 2B (1800 g, crude) as light yellow oil. HNMR: δ 9.46 (s, 5 H), 7.27-7.34 (m, 5 H), 6.50-6.65 (m, 1 H), 5.71 (s, 1 H), 5.10-5.15 (m, 2 H), 3.68-3.70 (m, 14 H), 3.58-3.61 (m, 6 H), 3.39 (s, 2 H), 2.55 (s, 6 H), 2.44 (s, 2 H).

General procedure for preparation of Compound 3B



[00441] To a solution of Compound 2B (375 g, 999 mmol, 83.0% purity, 1.00 eq) in DCM (1.80 L) is added HATU (570 g, 1.50 mol, 1.50 eq) and DIEA (258 g, 2.00 mol, 348 mL, 2.00 eq) at 0 °C, the mixture is stirred at 0 °C for 30 min, then Compound 1B (606 g, 1.20 mol, 1.20 eq) is added, the mixture is stirred at 25 °C for 1 hr. LCMS showed desired MS is given. The mixture is combined to one batch, then the mixture is diluted with DCM (5.00 L), washed with 1 N HCl aqueous solution (2.00 L*2), then the organic layer is washed with saturated Na₂CO₃ aqueous solution (2.00 L*2) and brine (2.00 L), the organic layer is dried over Na₂SO₄, filtered and concentrated under vacuum to give Compound 3B (3.88 kg, crude) as yellow oil.

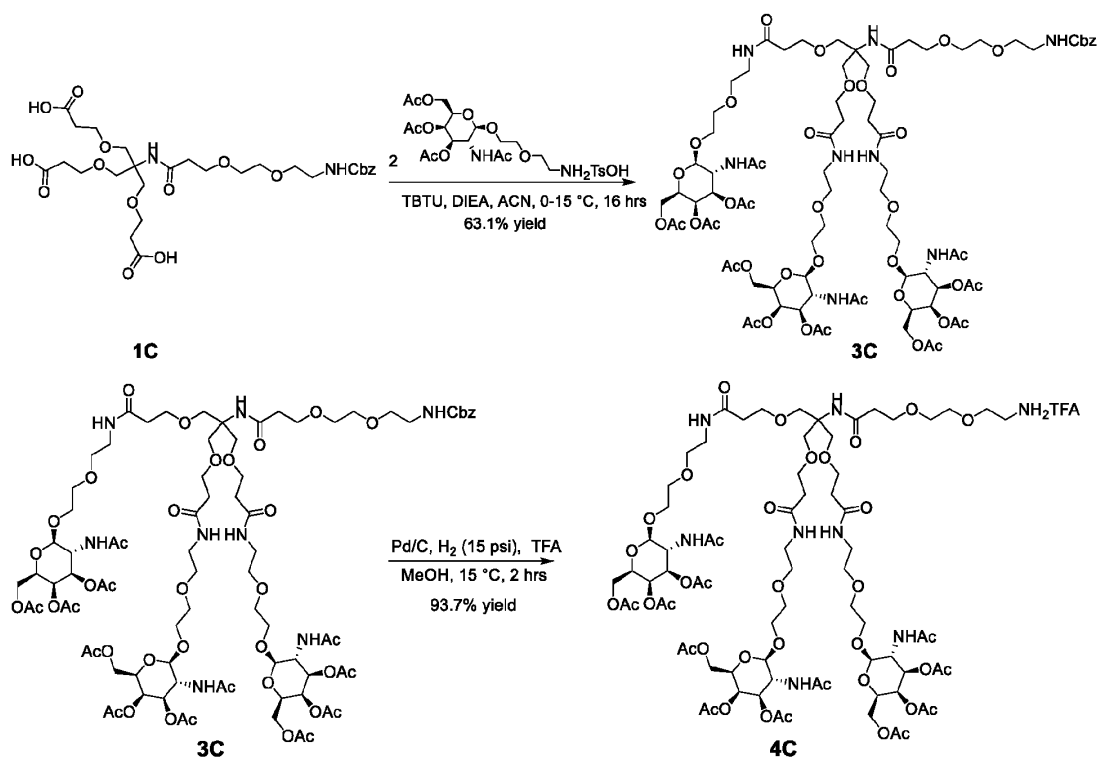
General procedure for preparation of TRIS-PEG2-CBZ.

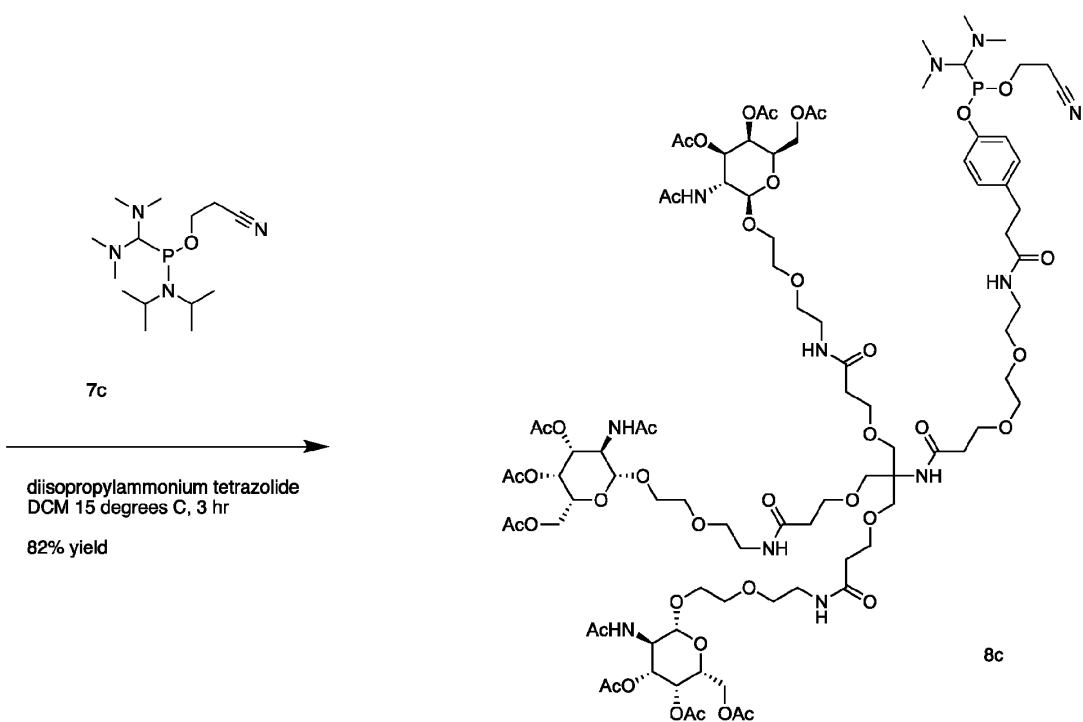
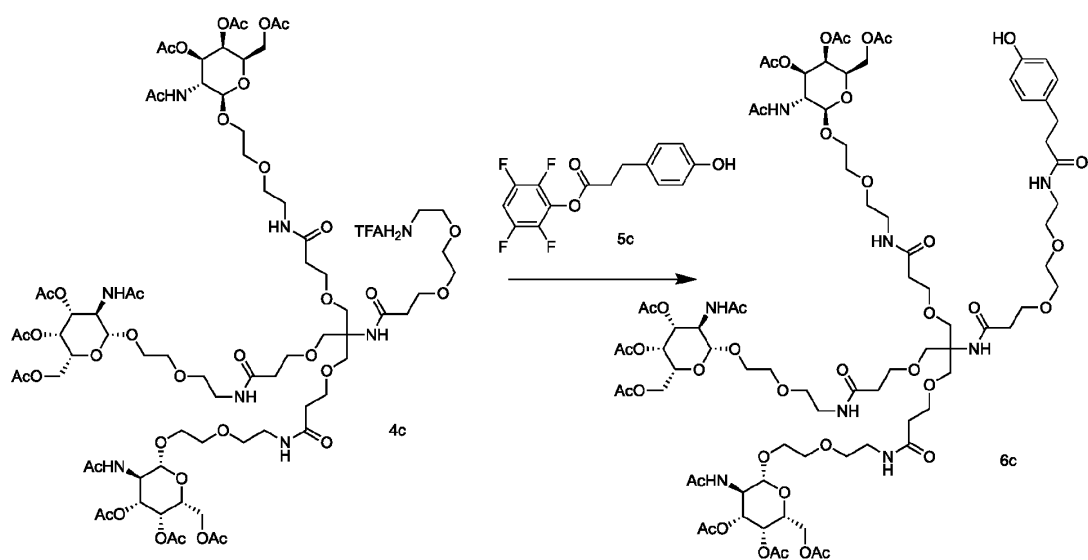
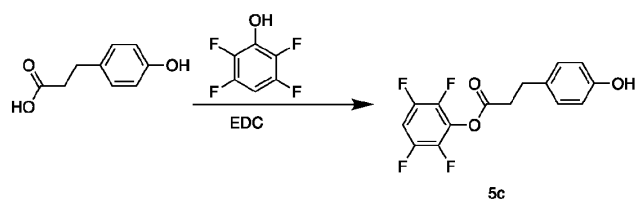


[00442] A solution of Compound 3B (775 g, 487 mmol, 50.3% purity, 1.00 eq) in HCl/dioxane (4 M, 2.91 L, 23.8 eq) is stirred at 25 °C for 2 hrs. LCMS showed the desired MS is given. The mixture is concentrated under vacuum to give a residue. Then the combined residue is diluted with DCM (5.00 L), adjusted to pH=8 with 2.5 M NaOH aqueous solution, and separated. The aqueous phase is extracted with DCM (3.00 L) again, then the aqueous solution is adjusted to pH=3 with 1 N HCl aqueous solution, then extracted with DCM (5.00 L*2), the combined organic layer is washed with brine (3.00 L), dried over Na₂SO₄, filtered and concentrated under vacuum. The crude is purified by column chromatography (SiO₂, DCM:MeOH=0:1-12:1, 0.1% HOAc, R_f=0.4). The residue is diluted with DCM (5.00 L), adjusted to pH=8 with 2.5 M NaOH aqueous solution, separated, the aqueous solution is extracted with DCM (3.00 L) again, then the aqueous solution is adjusted to pH=3 with 6 N HCl aqueous solution, extracted with DCM:MeOH=10:1 (5.00 L*2), the combined organic layer is washed with brine (2.00 L), dried over

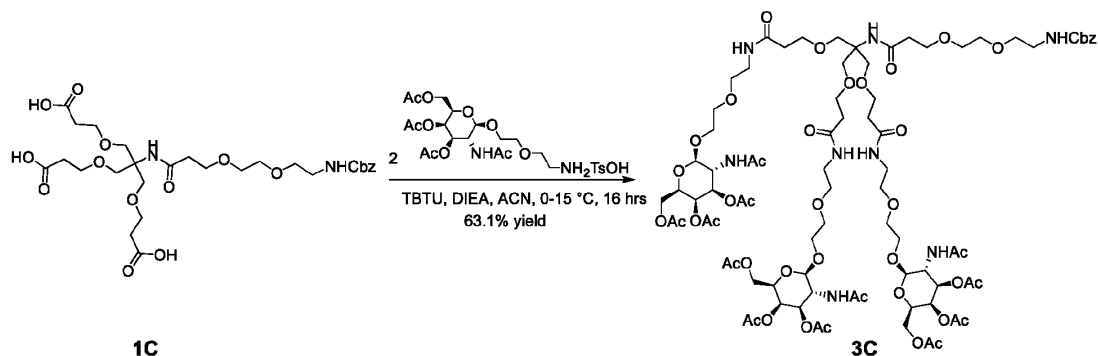
Na₂SO₄, filtered and concentrated under vacuum to give a residue. Then the residue is diluted with MeCN (5.00 L), concentrated under vacuum, repeat this procedure twice to remove water to give TRIS-PEG2-CBZ (1.25 kg, 1.91 mol, 78.1% yield, 95.8% purity) as light yellow oil. ¹HNMR: 400 MHz, MeOD, δ 7.30-7.35 (5 H), 5.07 (s, 2 H), 3.65-3.70 (m, 16 H), 3.59 (s, 4 H), 3.45 (t, *J*=5.6 Hz), 2.51 (t, *J*=6.0 Hz), 2.43 (t, 6.4 Hz).

[00443] Scheme for the preparation of TriNGal-TRIS-Peg2-Phosph 8c

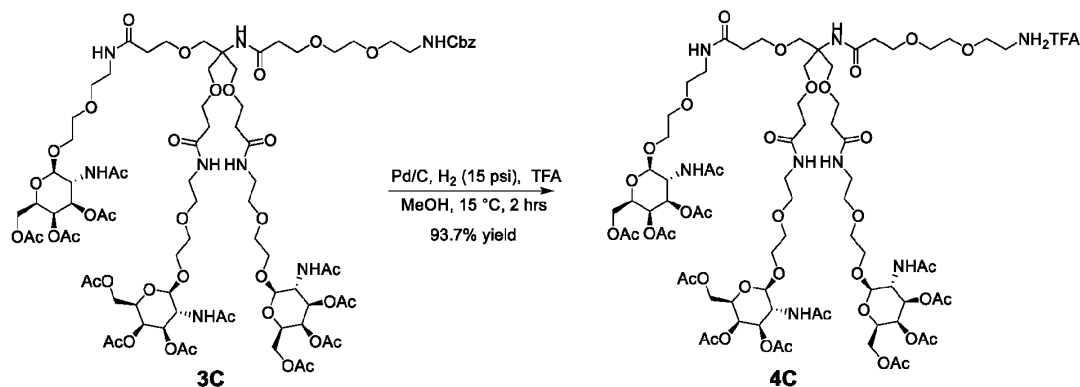




TriGNal-TRIS-Peg2-Phosph 8c

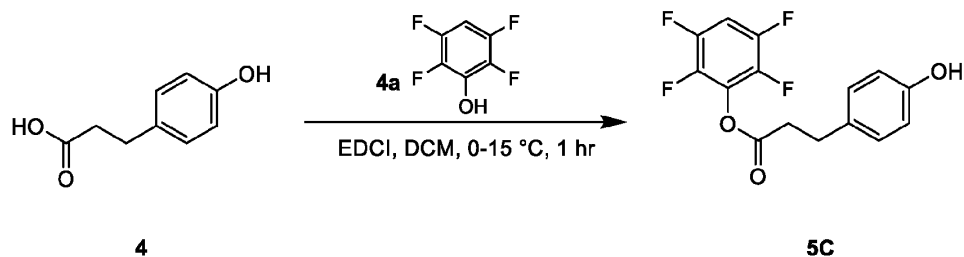
General procedure for preparation of Compound 3C

[00444] To a solution of Compound 1C (155 g, 245 mmol, 1.00 *eq*) in can (1500 mL) is added TBTU (260 g, 811 mmol, 3.30 *eq*), DIEA (209 g, 1.62 mol, 282 mL, 6.60 *eq*) and Compound 2C (492 g, 811 mmol, 3.30 *eq*, TsOH) at 0 °C, the mixture is stirred at 15 °C for 16 hrs. LCMS showed the desired MS is given. The mixture is concentrated under vacuum to give a residue, then the mixture is diluted with DCM (2000 mL), washed with 1 N HCl aqueous solution (700 mL * 2), then saturated NaHCO₃ aqueous solution (700 mL * 2) and concentrated under vacuum. The crude is purified by column chromatography to give Compound 3C (304 g, 155 mmol, 63.1% yield, 96.0% purity) as a yellow solid.

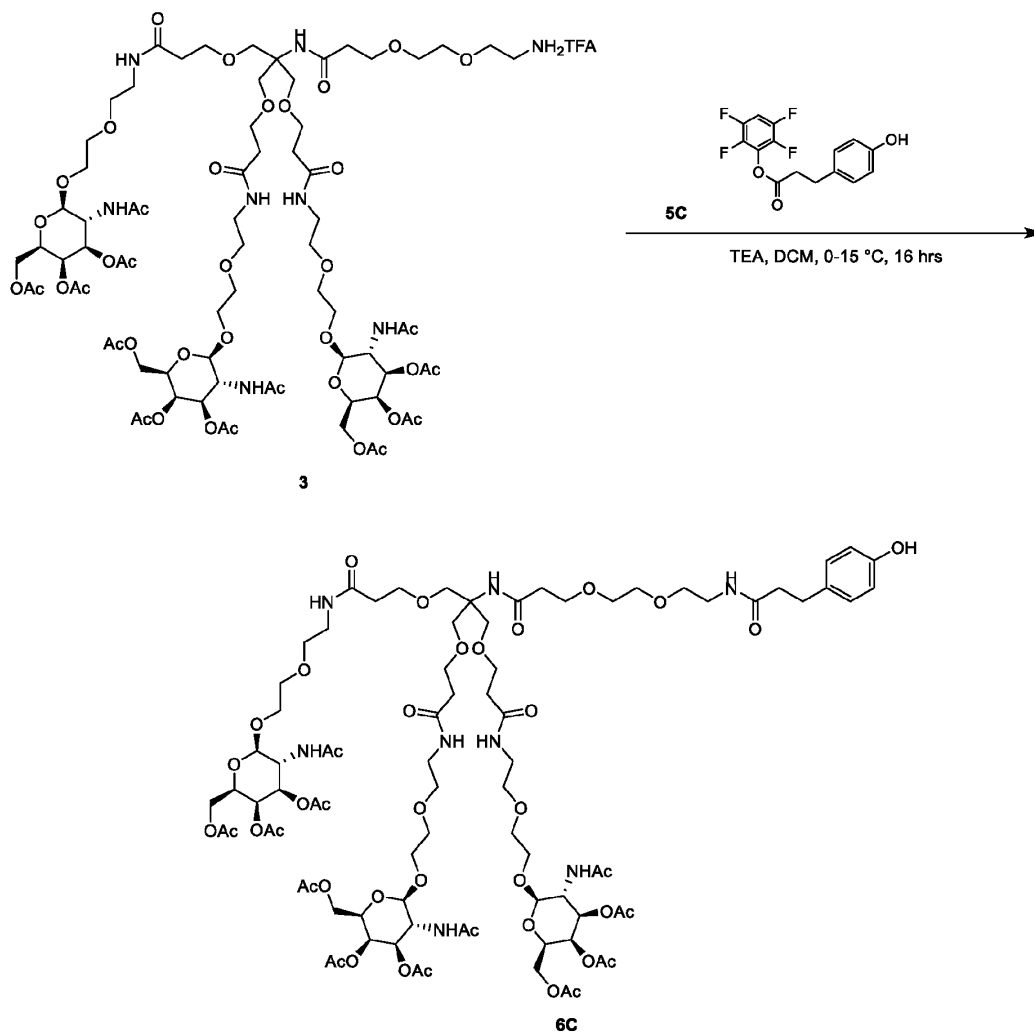
General procedure for preparation of Compound 4C

[00445] Two batches solution of Compound 3C (55.0 g, 29.2 mmol, 1.00 *eq*) in MeOH (1600 mL) is added Pd/C (6.60 g, 19.1 mmol, 10.0 % purity) and TFA (3.34 g, 29.2 mmol, 2.17 mL, 1.00 *eq*), the mixture is degassed under vacuum and purged with H₂. The mixture is stirred under H₂ (15 psi) at 15 °C for 2 hours. LCMS showed the desired MS is given. The mixture is filtered and the filtrate is concentrated under vacuum to give Compound 4C (106 g, 54.8 mmol, 93.7% yield, 96.2% purity, TFA) as a white solid.

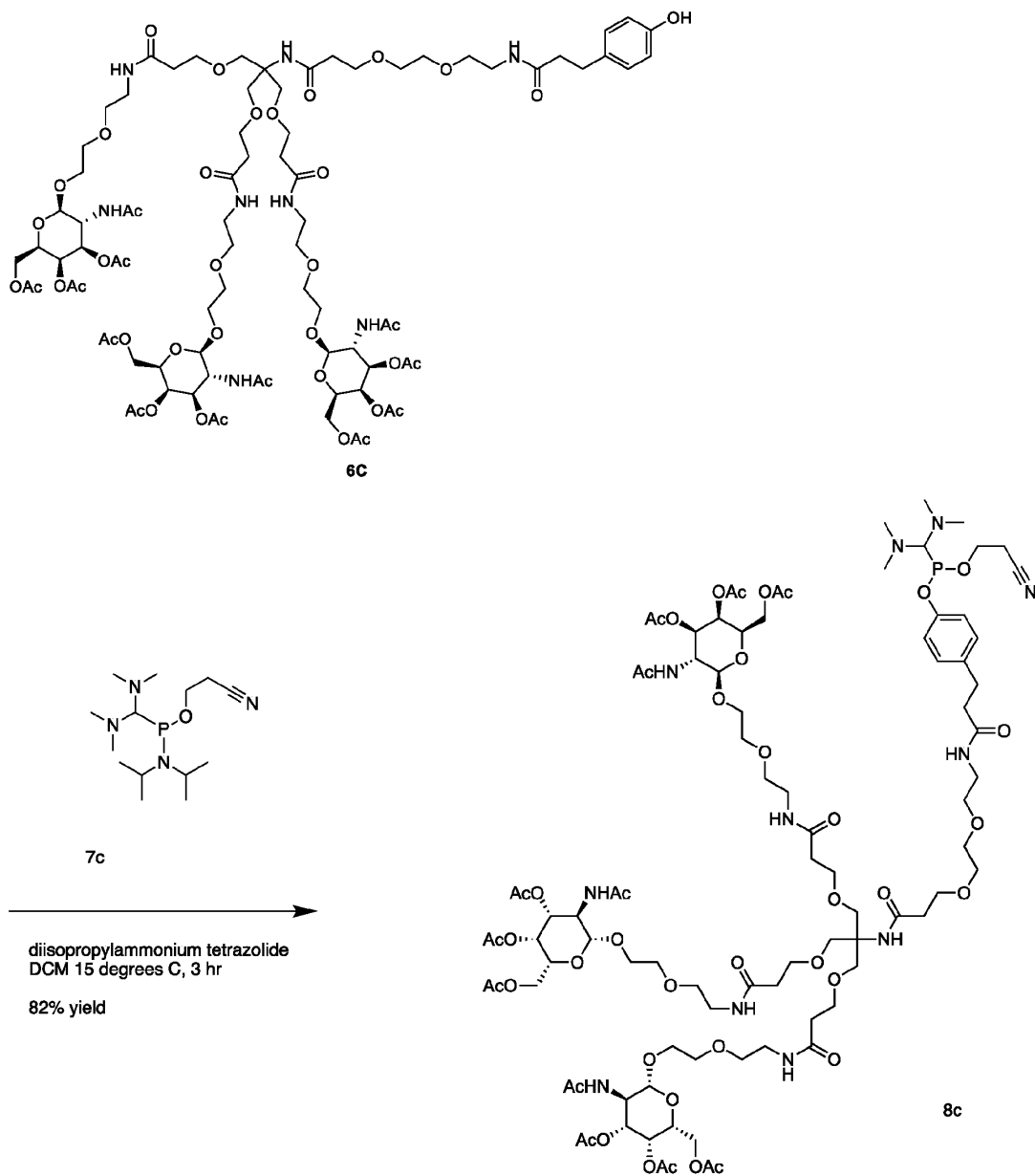
General procedure for preparation of compound 5C



[00446] Two batches in parallel. To a solution of EDCI (28.8 g, 150 mmol, 1.00 eq) in DCM (125 mL) is added compound **4a** (25.0 g, 150 mmol, 1.00 eq) dropwise at 0 °C, then the mixture is added to compound **4** (25.0 g, 150 mmol, 1.00 eq) in DCM (125 mL) at 0 °C, then the mixture is stirred at 25 °C for 1 hr. TLC (Petroleum ether : Ethyl acetate = 3 : 1, R_f = 0.45) showed the reactant is consumed and one new spot is formed. The reaction mixture is diluted with DCM (100 mL) then washed with aq. NaHCO₃ (250 mL * 1) and brine (250 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is purified by column chromatography (SiO₂, Petroleum ether : Ethyl acetate = 100 : 1 to 3 : 1), TLC (SiO₂, Petroleum ether : Ethyl acetate = 3 : 1), R_f = 0.45, then concentrated under reduced pressure to give a residue. Compound **5C** (57.0 g, 176 mmol, 58.4% yield, 96.9% purity) is obtained as colorless oil and confirmed ¹HNMR: EW33072-2-P1A, 400 MHz, DMSO δ 9.21 (s, 1 H), 7.07-7.09 (m, 2 H), 6.67-6.70 (m, 2 H), 3.02-3.04 (m, 2 H), 2.86-2.90 (m, 2 H)

General procedure for preparation of compound 6

[00447] To a mixture of compound **3** (79.0 g, 41.0 mmol, 96.4% purity, 1.00 eq, TFA) and compound **6C** (14.2 g, 43.8 mmol, 96.9% purity, 1.07 eq) in DCM (800 mL) is added TEA (16.6 g, 164 mmol, 22.8 mL, 4.00 eq) dropwise at 0 °C, the mixture is stirred at 15 °C for 16 hrs. LCMS (EW33072-12-P1B, Rt = 0.844 min) showed the desired mass is detected. The reaction mixture is diluted with DCM (400 mL) and washed with aq. NaHCO₃ (400 mL * 1) and brine (400 mL * 1), then the mixture is diluted with DCM (2.00 L) and washed with 0.7 M Na₂CO₃ (1000 mL * 3) and brine (800 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue is used to next step directly without purification. Compound **6** (80.0 g, crude) is obtained as white solid and confirmed via ¹HNMR: EW33072-12-P1A, 400 MHz, MeOD δ 7.-2 - 7.04 (m, 2 H), 6.-8 - 6.70 (m, 2 H), 5.-4 - 5.35 (s, 3 H), 5.-7 - 5.08 (d, J = 4.00 Hz, 3 H), 4.-2 - 4.64 (d, J = 8.00 Hz, 3 H), 3.-1 - 4.16 (m, 16 H), 3.-1 - 3.70 (m, 44 H), 2.-0 - 2.83 (m, 2 H), 2.68 (m, 2 H), 2.-6 - 2.47 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.-4 - 1.95 (d, J = 4.00 Hz, 18 H).

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

[00448] Two batches are synthesized in parallel. To a solution of compound **6c** (40.0 g, 21.1 mmol, 1.00 eq) in DCM (600 mL) is added diisopropylammonium tetrazolide (3.62 g, 21.1 mmol, 1.00 eq) and compound **7c** (6.37 g, 21.1 mmol, 6.71 mL, 1.00 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 1 hr, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 30 mins, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 1.5 hrs. LCMS (EW33072-17-P1C1, Rt = 0.921 min) showed the desired MS+1 is detected. LCMS (EW33072-17-P1C2, Rt = 0.919 min) showed the desired MS+1 is detected. Two batches are combined for work-up. The mixture is

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

[00449] δ 7.13-7.15 (d, J = 8.50 Hz, 2 H), 6.95-6.97 (dd, J = 8.38, 1.13 Hz, 2 H), 5.34 (d, J = 2.88 Hz, 3 H), .09 (dd, J = 11.26, 3.38 Hz, 3 H), 4.64 (d, J = 8.50 Hz, 3 H), 3.-9 - 4.20 (m, 12 H), 3.-8 - 3.98 (m, 5 H), 3.-6 - 3.83 (m, 20 H), 3.-1 - 3.65 (m, 17 H), 3.-3 - 3.50 (m, 9 H), 2.87 (t, J = 7.63 Hz, 2 H), 2.76 (t, J = 5.94 Hz, 2 H), 2.-2 - 2.50 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.-4 - 1.95 (d, J = 6.13 Hz, 18 H), 1.24-1.26 (d, J = 6.75 Hz, 6 H), 1.18-1.20 (d, J = 6.75 Hz, 6 H)

Example 26: Modification motif 1

[00450] An example FGG siRNA includes a combination of the following modifications:

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

Example 27: Modification motif 2

[00451] An example FGG siRNA includes a combination of the following modifications:

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

IV. SEQUENCE INFORMATION

[00452] Some embodiments include one or more nucleic acid sequences in the following tables:

Table 78. Sequence information

SEQ ID NO:	Description
1-1742	FGG siRNA sense strand sequences
1743-3484	FGG siRNA antisense strand sequences
3485-3537	Modified FGG siRNA sense strand sequences
3538-3590	Modified FGG siRNA antisense strand sequences
3591-3594	Modified FGG siRNA sense strand sequences
3595-3598	Modified FGG siRNA antisense strand sequences
3599-3620	Modified FGG siRNA sense strand sequences
3621	Full-length human FGG mRNA sequence (Ensembl Acc. No. ENST00000404648)
3622-3630	Modification pattern 1S to 9S
3631-3639	Modification pattern 1AS to 9AS

SEQ ID NO:	Description
3640	Modification pattern ASO1
3641-3676	Modified FGG siRNA sense sequences
3677-3712	Modified FGG siRNA antisense sequences
3713-3748	FGG siRNA sense strand sequences
3749-3784	FGG siRNA antisense sequences
3785-3804	Modification pattern 10S to 29S
3805-3816	Modification pattern 10AS to 21AS

Table 79. siRNA sequences

siRNA Name	SEQ ID NO:	Sense strand sequence (5'-3')	SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 1	1	AAAAAGGAGGAGCTTCAAC	1743	GTTGAAGCTCCTCCTTTTT
siRNA 2	2	AAAAGGAGGAGCTTCAACC	1744	GGTTGAAGCTCCTCCTTTT
siRNA 3	3	AAAGGAGGAGCTTCAACCT	1745	AGGTTGAAGCTCCTCCTTT
siRNA 4	4	AAGGAGGAGCTTCAACCTG	1746	CAGGTTGAAGCTCCTCCTT
siRNA 5	5	AGGAGGAGCTTCAACCTGT	1747	ACAGGTTGAAGCTCCTCCT
siRNA 6	6	GGAGGAGCTTCAACCTGTG	1748	CACAGGTTGAAGCTCCTCC
siRNA 7	7	GAGGAGCTTCAACCTGTGT	1749	ACACAGGTTGAAGCTCCTC
siRNA 8	8	AGGAGCTTCAACCTGTGTG	1750	CACACAGGTTGAAGCTCCT
siRNA 9	9	GGAGCTTCAACCTGTGTGC	1751	GCACACAGGTTGAAGCTCC
siRNA 10	10	GAGCTTCAACCTGTGTGCA	1752	TGCACACAGGTTGAAGCTC
siRNA 11	11	AGCTTCAACCTGTGTGCAA	1753	TTGCACACAGGTTGAAGCT
siRNA 12	12	GCTTCAACCTGTGTGCAAA	1754	TTTGCACACAGGTTGAAGC
siRNA 13	13	CTTCAACCTGTGTGCAAAA	1755	TTTTGCACACAGGTTGAAG
siRNA 14	14	TTCAACCTGTGTGCAAAAT	1756	ATTTTGCACACAGGTTGAA
siRNA 15	15	TCAACCTGTGTGCAAAATC	1757	GATTTTGCACACAGGTTGA
siRNA 16	16	CAACCTGTGTGCAAAATCT	1758	AGATTTTGCACACAGGTTG
siRNA 17	17	AACCTGTGTGCAAAATCTG	1759	CAGATTTTGCACACAGGTT
siRNA 18	18	ACCTGTGTGCAAAATCTGG	1760	CCAGATTTTGCACACAGGT
siRNA 19	19	CCTGTGTGCAAAATCTGGG	1761	CCCAGATTTTGCACACAGG
siRNA 20	20	CTGTGTGCAAAATCTGGGA	1762	TCCCAGATTTTGCACACAG
siRNA 21	21	TGTGTGCAAAATCTGGGAA	1763	TTCCCAGATTTTGCACACA
siRNA 22	22	GTGTGCAAAATCTGGGAAC	1764	GTTCCCAGATTTTGCACAC
siRNA 23	23	TGTGCAAAATCTGGGAACC	1765	GGTCCCAGATTTTGCACA
siRNA 24	24	GTGCAAAATCTGGGAACCT	1766	AGGTTCCCAGATTTTGCAC
siRNA 25	25	TGCAAAATCTGGGAACCTG	1767	CAGGTTCCCAGATTTTGC
siRNA 26	26	GCAAAATCTGGGAACCTGA	1768	TCAGGTTCCCAGATTTTGC
siRNA 27	27	CAAAATCTGGGAACCTGAC	1769	GTCAGGTTCCCAGATTTTG
siRNA 28	28	AAAATCTGGGAACCTGACA	1770	TGTCAGGTTCCCAGATTTT
siRNA 29	29	AAATCTGGGAACCTGACAG	1771	CTGTCAGGTTCCCAGATTT
siRNA 30	30	AATCTGGGAACCTGACAGT	1772	ACTGTCAGGTTCCCAGATT
siRNA 31	31	ATCTGGGAACCTGACAGTA	1773	TACTGTCAGGTTCCCAGAT
siRNA 32	32	TCTGGGAACCTGACAGTAT	1774	ATACTGTCAGGTTCCCAGA
siRNA 33	33	CTGGGAACCTGACAGTATA	1775	TATACTGTCAGGTTCCCAG
siRNA 34	34	TGGGAACCTGACAGTATAG	1776	CTATACTGTCAGGTTCCCA
siRNA 35	35	GGGAACCTGACAGTATAGG	1777	CCTATACTGTCAGGTTCCC
siRNA 36	36	GGAACCTGACAGTATAGGT	1778	ACCTATACTGTCAGGTTCC
siRNA 37	37	GAACCTGACAGTATAGGTT	1779	AACCTATACTGTCAGGTTCC
siRNA 38	38	AACCTGACAGTATAGGTTG	1780	CAACCTATACTGTCAGGTT

siRNA 39	39	ACCTGACAGTATAGGTTGG	1781	CCAACCTATACTGTCAGGT
siRNA 40	40	CCTGACAGTATAGGTTGGG	1782	CCCAACCTATACTGTCAGG
siRNA 41	41	CTGACAGTATAGGTTGGGG	1783	CCCCAACCTATACTGTCAG
siRNA 42	42	TGACAGTATAGGTTGGGGG	1784	CCCCCAACCTATACTGTCA
siRNA 43	43	GACAGTATAGGTTGGGGGC	1785	GCCCCCAACCTATACTGTC
siRNA 44	44	ACAGTATAGGTTGGGGGCC	1786	GGCCCCCAACCTATACTGT
siRNA 45	45	CAGTATAGGTTGGGGGCCA	1787	TGGCCCCCAACCTATACTG
siRNA 46	46	AGTATAGGTTGGGGGCCAG	1788	CTGGCCCCCAACCTATACT
siRNA 47	47	GTATAGGTTGGGGGCCAGG	1789	CCTGGCCCCCAACCTATAC
siRNA 48	48	TATAGGTTGGGGGCCAGGA	1790	TCCTGGCCCCCAACCTATA
siRNA 49	49	ATAGGTTGGGGGCCAGGAT	1791	ATCCTGGCCCCCAACCTAT
siRNA 50	50	TAGGTTGGGGGCCAGGATG	1792	CATCCTGGCCCCCAACCTA
siRNA 51	51	AGGTTGGGGGCCAGGATGA	1793	TCATCCTGGCCCCCAACCT
siRNA 52	52	GGTTGGGGGCCAGGATGAG	1794	CTCATCCTGGCCCCCAACC
siRNA 53	53	GTTGGGGGCCAGGATGAGG	1795	CCTCATCCTGGCCCCCAAC
siRNA 54	54	TTGGGGGCCAGGATGAGGA	1796	TCCTCATCCTGGCCCCCAA
siRNA 55	55	TGGGGGCCAGGATGAGGAA	1797	TTCTCATCCTGGCCCCCA
siRNA 56	56	GGGGGCCAGGATGAGGAAA	1798	TTTCTCATCCTGGCCCCC
siRNA 57	57	GGGGCCAGGATGAGGAAAA	1799	TTTTCTCATCCTGGCCCC
siRNA 58	58	GGGCCAGGATGAGGAAAAA	1800	TTTTCTCATCCTGGCCCC
siRNA 59	59	GGCCAGGATGAGGAAAAAG	1801	CTTTTCTCATCCTGGGCC
siRNA 60	60	GCCAGGATGAGGAAAAAGG	1802	CCTTTTCTCATCCTGGGC
siRNA 61	61	CCAGGATGAGGAAAAAGGA	1803	TCCTTTTCTCATCCTGG
siRNA 62	62	CAGGATGAGGAAAAAGGAA	1804	TTCCTTTTCTCATCCTG
siRNA 63	63	AGGATGAGGAAAAAGGAAC	1805	GTTCTTTTCTCATCCT
siRNA 64	64	GGATGAGGAAAAAGGAACG	1806	CGTTCCTTTTCTCATCC
siRNA 65	65	GATGAGGAAAAAGGAACGG	1807	CCGTTCTTTTCTCATC
siRNA 66	66	ATGAGGAAAAAGGAACGGG	1808	CCCGTTCCTTTTCTCAT
siRNA 67	67	TGAGGAAAAAGGAACGGGA	1809	TCCCGTTCCTTTTCTCA
siRNA 68	68	GAGGAAAAAGGAACGGGAA	1810	TTCCCGTTCCTTTTCTC
siRNA 69	69	AGGAAAAAGGAACGGGAAA	1811	TTTCCCGTTCCTTTTCT
siRNA 70	70	GGAAAAAGGAACGGGAAAG	1812	CTTTCCCGTTCCTTTTCC
siRNA 71	71	GAAAAAGGAACGGGAAAGA	1813	TCTTTCCCGTTCCTTTTC
siRNA 72	72	AAAAAGGAACGGGAAAGAC	1814	GTCTTTCCCGTTCCTTTT
siRNA 73	73	AAAAGGAACGGGAAAGACC	1815	GGTCTTTCCCGTTCCTTT
siRNA 74	74	AAAGGAACGGGAAAGACCT	1816	AGGTCTTTCCCGTTCCTT
siRNA 75	75	AAGGAACGGGAAAGACCTG	1817	CAGGTCTTTCCCGTTCCT
siRNA 76	76	AGGAACGGGAAAGACCTGC	1818	GCAGGTCTTTCCCGTTCCT
siRNA 77	77	GGAACGGGAAAGACCTGCC	1819	GGCAGGTCTTTCCCGTTC
siRNA 78	78	GAACGGGAAAGACCTGCC	1820	GGGCAGGTCTTTCCCGTTC
siRNA 79	79	AACGGGAAAGACCTGCCCA	1821	TGGGCAGGTCTTTCCCGTT
siRNA 80	80	ACGGGAAAGACCTGCCAC	1822	GTGGGCAGGTCTTTCCCGT
siRNA 81	81	CGGGAAAGACCTGCCACC	1823	GGTGGGCAGGTCTTTCCCG
siRNA 82	82	GGGAAAGACCTGCCACCC	1824	GGGTGGGCAGGTCTTTCCC
siRNA 83	83	GGAAAGACCTGCCACCCT	1825	AGGGTGGGCAGGTCTTTCC
siRNA 84	84	GAAAGACCTGCCACCCTT	1826	AAGGGTGGGCAGGTCTTTC
siRNA 85	85	AAAGACCTGCCACCCTTTC	1827	GAAGGGTGGGCAGGTCTTT
siRNA 86	86	AAGACCTGCCACCCTTCT	1828	AGAAGGGTGGGCAGGTCTT
siRNA 87	87	AGACCTGCCACCCTTCTG	1829	CAGAAGGGTGGGCAGGTCT
siRNA 88	88	GACCTGCCACCCTTCTGG	1830	CCAGAAGGGTGGGCAGGTCT
siRNA 89	89	ACCTGCCACCCTTCTGGT	1831	ACCAGAAGGGTGGGCAGGT
siRNA 90	90	CCTGCCACCCTTCTGGTA	1832	TACCAGAAGGGTGGGCAGG

siRNA 91	91	CTGCCCACCCCTTCTGGTAA	1833	TTACCAGAAGGGTGGGCAG
siRNA 92	92	TGCCCACCCCTTCTGGTAAG	1834	CTTACCAGAAGGGTGGGCA
siRNA 93	93	GCCCACCCCTTCTGGTAAGG	1835	CCTTACCAGAAGGGTGGGC
siRNA 94	94	CCCACCCCTTCTGGTAAGGA	1836	TCCTTACCAGAAGGGTGGG
siRNA 95	95	CCACCCCTTCTGGTAAGGAG	1837	CTCCTTACCAGAAGGGTGG
siRNA 96	96	CACCCCTTCTGGTAAGGAGG	1838	CCTCCTTACCAGAAGGGTG
siRNA 97	97	ACCCCTTCTGGTAAGGAGGC	1839	GCCTCCTTACCAGAAGGGT
siRNA 98	98	CCCTTCTGGTAAGGAGGCC	1840	GGCCTCCTTACCAGAAGGG
siRNA 99	99	CCTTCTGGTAAGGAGGCC	1841	GGGCCTCCTTACCAGAAGG
siRNA 100	100	CTTCTGGTAAGGAGGCC	1842	GGGGCCTCCTTACCAGAAG
siRNA 101	101	TTCTGGTAAGGAGGCCCG	1843	CGGGGCCTCCTTACCAGAA
siRNA 102	102	TCTGGTAAGGAGGCCCGT	1844	ACGGGGCCTCCTTACCAGA
siRNA 103	103	CTGGTAAGGAGGCCCGTG	1845	CACGGGGCCTCCTTACCAG
siRNA 104	104	TGGTAAGGAGGCCCGTGAT	1846	TCACGGGGCCTCCTTACCA
siRNA 105	105	GGTAAGGAGGCCCGTGAT	1847	ATCACGGGGCCTCCTTACC
siRNA 106	106	GTAAGGAGGCCCGTGATC	1848	GATCACGGGGCCTCCTTAC
siRNA 107	107	TAAGGAGGCCCGTGATCA	1849	TGATCACGGGGCCTCCTTA
siRNA 108	108	AAGGAGGCCCGTGATCAG	1850	CTGATCACGGGGCCTCCTT
siRNA 109	109	AGGAGGCCCGTGATCAGC	1851	GCTGATCACGGGGCCTCCT
siRNA 110	110	GGAGGCCCGTGATCAGCT	1852	AGCTGATCACGGGGCCTCC
siRNA 111	111	GAGGCCCGTGATCAGCTC	1853	GAGCTGATCACGGGGCCTC
siRNA 112	112	AGGCCCGTGATCAGCTCC	1854	GGAGCTGATCACGGGGCCT
siRNA 113	113	GGGCCCGTGATCAGCTCCA	1855	TGGAGCTGATCACGGGGCC
siRNA 114	114	GCCCCGTGATCAGCTCCAG	1856	CTGGAGCTGATCACGGGGC
siRNA 115	115	CCCCGTGATCAGCTCCAGC	1857	GCTGGAGCTGATCACGGGG
siRNA 116	116	CCCGTGATCAGCTCCAGCC	1858	GGCTGGAGCTGATCACGGG
siRNA 117	117	CCGTGATCAGCTCCAGCCA	1859	TGGCTGGAGCTGATCACGG
siRNA 118	118	CGTGATCAGCTCCAGCCAT	1860	ATGGCTGGAGCTGATCACG
siRNA 119	119	GTGATCAGCTCCAGCCATT	1861	AATGGCTGGAGCTGATCAC
siRNA 120	120	TGATCAGCTCCAGCCATTT	1862	AAATGGCTGGAGCTGATCA
siRNA 121	121	GATCAGCTCCAGCCATTTG	1863	CAAATGGCTGGAGCTGATC
siRNA 122	122	ATCAGCTCCAGCCATTTGC	1864	GCAAATGGCTGGAGCTGAT
siRNA 123	123	TCAGCTCCAGCCATTTGCA	1865	TGCAAATGGCTGGAGCTGA
siRNA 124	124	CAGCTCCAGCCATTTGCAG	1866	CTGCAAATGGCTGGAGCTG
siRNA 125	125	AGCTCCAGCCATTTGCAGT	1867	ACTGCAAATGGCTGGAGCT
siRNA 126	126	GCTCCAGCCATTTGCAGTC	1868	GACTGCAAATGGCTGGAGC
siRNA 127	127	CTCCAGCCATTTGCAGTCC	1869	GGACTGCAAATGGCTGGAG
siRNA 128	128	TCCAGCCATTTGCAGTCCT	1870	AGGACTGCAAATGGCTGGA
siRNA 129	129	CCAGCCATTTGCAGTCCTG	1871	CAGGACTGCAAATGGCTGG
siRNA 130	130	CAGCCATTTGCAGTCCTGG	1872	CCAGGACTGCAAATGGCTG
siRNA 131	131	AGCCATTTGCAGTCCTGGC	1873	GCCAGGACTGCAAATGGCT
siRNA 132	132	GCCATTTGCAGTCCTGGCT	1874	AGCCAGGACTGCAAATGGC
siRNA 133	133	CCATTTGCAGTCCTGGCTA	1875	TAGCCAGGACTGCAAATGG
siRNA 134	134	CATTTGCAGTCCTGGCTAT	1876	ATAGCCAGGACTGCAAATG
siRNA 135	135	ATTTGCAGTCCTGGCTATC	1877	GATAGCCAGGACTGCAAAT
siRNA 136	136	TTTGCAGTCCTGGCTATCC	1878	GGATAGCCAGGACTGCAAA
siRNA 137	137	TTGCAGTCCTGGCTATCCC	1879	GGGATAGCCAGGACTGCAA
siRNA 138	138	TGCAGTCCTGGCTATCCCA	1880	TGGGATAGCCAGGACTGCA
siRNA 139	139	GCAGTCCTGGCTATCCCAG	1881	CTGGGATAGCCAGGACTGC
siRNA 140	140	CAGTCCTGGCTATCCCAGG	1882	CCTGGGATAGCCAGGACTG
siRNA 141	141	AGTCCTGGCTATCCCAGGA	1883	TCCTGGGATAGCCAGGACT
siRNA 142	142	GTCCTGGCTATCCCAGGAG	1884	CTCCTGGGATAGCCAGGAC

siRNA 143	143	TCCTGGCTATCCCAGGAGC	1885	GCTCCTGGGATAGCCAGGA
siRNA 144	144	CCTGGCTATCCCAGGAGCT	1886	AGCTCCTGGGATAGCCAGG
siRNA 145	145	CTGGCTATCCCAGGAGCTT	1887	AAGCTCCTGGGATAGCCAG
siRNA 146	146	TGGCTATCCCAGGAGCTTA	1888	TAAGCTCCTGGGATAGCCA
siRNA 147	147	GGCTATCCCAGGAGCTTAC	1889	GTAAGCTCCTGGGATAGCC
siRNA 148	148	GCTATCCCAGGAGCTTACA	1890	TGTAAGCTCCTGGGATAGC
siRNA 149	149	CTATCCCAGGAGCTTACAT	1891	ATGTAAGCTCCTGGGATAG
siRNA 150	150	TATCCCAGGAGCTTACATA	1892	TATGTAAGCTCCTGGGATA
siRNA 151	151	ATCCCAGGAGCTTACATAA	1893	TTATGTAAGCTCCTGGGAT
siRNA 152	152	TCCCAGGAGCTTACATAAA	1894	TTTATGTAAGCTCCTGGGA
siRNA 153	153	CCCAGGAGCTTACATAAAG	1895	CTTTATGTAAGCTCCTGGG
siRNA 154	154	CCAGGAGCTTACATAAAGG	1896	CCTTTATGTAAGCTCCTGG
siRNA 155	155	CAGGAGCTTACATAAAGGG	1897	CCCTTTATGTAAGCTCCTG
siRNA 156	156	AGGAGCTTACATAAAGGGA	1898	TCCCTTTATGTAAGCTCCT
siRNA 157	157	GGAGCTTACATAAAGGGAC	1899	GTCCCTTTATGTAAGCTCC
siRNA 158	158	GAGCTTACATAAAGGGACA	1900	TGTCCCTTTATGTAAGCTC
siRNA 159	159	AGCTTACATAAAGGGACAA	1901	TTGTCCCTTTATGTAAGCT
siRNA 160	160	GCTTACATAAAGGGACAAT	1902	ATTGTCCCTTTATGTAAGC
siRNA 161	161	CTTACATAAAGGGACAATT	1903	AATTGTCCCTTTATGTAAG
siRNA 162	162	TTACATAAAGGGACAATTG	1904	CAATTGTCCCTTTATGTAA
siRNA 163	163	TACATAAAGGGACAATTGG	1905	CCAATTGTCCCTTTATGTA
siRNA 164	164	ACATAAAGGGACAATTGGA	1906	TCCAATTGTCCCTTTATGT
siRNA 165	165	CATAAAGGGACAATTGGAG	1907	CTCCAATTGTCCCTTTATG
siRNA 166	166	ATAAAGGGACAATTGGAGC	1908	GCTCCAATTGTCCCTTTAT
siRNA 167	167	TAAAGGGACAATTGGAGCC	1909	GGCTCCAATTGTCCCTTTA
siRNA 168	168	AAAGGGACAATTGGAGCCT	1910	AGGCTCCAATTGTCCCTTT
siRNA 169	169	AAGGGACAATTGGAGCCTG	1911	CAGGCTCCAATTGTCCCTT
siRNA 170	170	AGGGACAATTGGAGCCTGA	1912	TCAGGCTCCAATTGTCCCT
siRNA 171	171	GGGACAATTGGAGCCTGAG	1913	CTCAGGCTCCAATTGTCCC
siRNA 172	172	GGACAATTGGAGCCTGAGA	1914	TCTCAGGCTCCAATTGTCC
siRNA 173	173	GACAATTGGAGCCTGAGAG	1915	CTCTCAGGCTCCAATTGTC
siRNA 174	174	ACAATTGGAGCCTGAGAGG	1916	CCTCTCAGGCTCCAATTGT
siRNA 175	175	CAATTGGAGCCTGAGAGGT	1917	ACCTCTCAGGCTCCAATTG
siRNA 176	176	AATTGGAGCCTGAGAGGTG	1918	CACCTCTCAGGCTCCAATT
siRNA 177	177	ATTGGAGCCTGAGAGGTGA	1919	TCACCTCTCAGGCTCCAAT
siRNA 178	178	TTGGAGCCTGAGAGGTGAC	1920	GTCACCTCTCAGGCTCCAA
siRNA 179	179	TGGAGCCTGAGAGGTGACA	1921	TGTCACCTCTCAGGCTCCA
siRNA 180	180	GGAGCCTGAGAGGTGACAG	1922	CTGTCACCTCTCAGGCTCC
siRNA 181	181	GAGCCTGAGAGGTGACAGT	1923	ACTGTCACCTCTCAGGCTC
siRNA 182	182	AGCCTGAGAGGTGACAGTG	1924	CACCTGTCACCTCTCAGGCT
siRNA 183	183	GCCTGAGAGGTGACAGTGC	1925	GCACTGTCACCTCTCAGGC
siRNA 184	184	CCTGAGAGGTGACAGTGCT	1926	AGCACTGTCACCTCTCAGG
siRNA 185	185	CTGAGAGGTGACAGTGCTG	1927	CAGCACTGTCACCTCTCAG
siRNA 186	186	TGAGAGGTGACAGTGCTGA	1928	TCAGCACTGTCACCTCTCA
siRNA 187	187	GAGAGGTGACAGTGCTGAC	1929	GTCAGCACTGTCACCTCTC
siRNA 188	188	AGAGGTGACAGTGCTGACA	1930	TGTCAGCACTGTCACCTCT
siRNA 189	189	GAGGTGACAGTGCTGACAC	1931	GTGTCAGCACTGTCACCTC
siRNA 190	190	AGGTGACAGTGCTGACACT	1932	AGTGTGTCAGCACTGTCACCT
siRNA 191	191	GGTGACAGTGCTGACACTA	1933	TAGTGTGTCAGCACTGTCACC
siRNA 192	192	GTGACAGTGCTGACACTAC	1934	GTAGTGTGTCAGCACTGTCAC
siRNA 193	193	TGACAGTGCTGACACTACA	1935	TGTAGTGTGTCAGCACTGTCA
siRNA 194	194	GACAGTGCTGACACTACAA	1936	TTGTAGTGTGTCAGCACTGTC

siRNA 195	195	ACAGTGCTGACACTACAAG	1937	CTTGTAAGTGTGACACTGT
siRNA 196	196	CAGTGCTGACACTACAAGG	1938	CCTTGTAAGTGTGACACTG
siRNA 197	197	AGTGCTGACACTACAAGGC	1939	GCCTTGTAAGTGTGACACT
siRNA 198	198	GTGCTGACACTACAAGGCT	1940	AGCCTTGTAAGTGTGACAC
siRNA 199	199	TGCTGACACTACAAGGCTC	1941	GAGCCTTGTAAGTGTGACCA
siRNA 200	200	GCTGACACTACAAGGCTCG	1942	CGAGCCTTGTAAGTGTGACG
siRNA 201	201	CTGACACTACAAGGCTCGG	1943	CCGAGCCTTGTAAGTGTGAC
siRNA 202	202	TGACACTACAAGGCTCGGA	1944	TCCGAGCCTTGTAAGTGTCA
siRNA 203	203	GACACTACAAGGCTCGGAG	1945	CTCCGAGCCTTGTAAGTGTG
siRNA 204	204	ACACTACAAGGCTCGGAGC	1946	GCTCCGAGCCTTGTAAGTGT
siRNA 205	205	CACTACAAGGCTCGGAGCT	1947	AGCTCCGAGCCTTGTAAGTG
siRNA 206	206	ACTACAAGGCTCGGAGCTC	1948	GAGCTCCGAGCCTTGTAAGT
siRNA 207	207	CTACAAGGCTCGGAGCTCC	1949	GGAGCTCCGAGCCTTGTAAG
siRNA 208	208	TACAAGGCTCGGAGCTCCG	1950	CGGAGCTCCGAGCCTTGTA
siRNA 209	209	ACAAGGCTCGGAGCTCCGG	1951	CCGGAGCTCCGAGCCTTGT
siRNA 210	210	CAAGGCTCGGAGCTCCGGG	1952	CCCGGAGCTCCGAGCCTTG
siRNA 211	211	AAGGCTCGGAGCTCCGGGC	1953	GCCCGGAGCTCCGAGCCTT
siRNA 212	212	AGGCTCGGAGCTCCGGGCA	1954	TGCCCGGAGCTCCGAGCCT
siRNA 213	213	GGCTCGGAGCTCCGGGCAC	1955	GTGCCCGGAGCTCCGAGCC
siRNA 214	214	GCTCGGAGCTCCGGGCACT	1956	AGTGCCCGGAGCTCCGAGC
siRNA 215	215	CTCGGAGCTCCGGGCACTC	1957	GAGTGCCCGGAGCTCCGAG
siRNA 216	216	TCGGAGCTCCGGGCACTCA	1958	TGAGTGCCCGGAGCTCCGA
siRNA 217	217	CGGAGCTCCGGGCACTCAG	1959	CTGAGTGCCCGGAGCTCCG
siRNA 218	218	GGAGCTCCGGGCACTCAGA	1960	TCTGAGTGCCCGGAGCTCC
siRNA 219	219	GAGCTCCGGGCACTCAGAC	1961	GTCTGAGTGCCCGGAGCTC
siRNA 220	220	AGCTCCGGGCACTCAGACA	1962	TGTCTGAGTGCCCGGAGCT
siRNA 221	221	GCTCCGGGCACTCAGACAT	1963	ATGTCTGAGTGCCCGGAGC
siRNA 222	222	CTCCGGGCACTCAGACATC	1964	GATGTCTGAGTGCCCGGAG
siRNA 223	223	TCCGGGCACTCAGACATCA	1965	TGATGTCTGAGTGCCCGGA
siRNA 224	224	CCGGGCACTCAGACATCAT	1966	ATGATGTCTGAGTGCCCGG
siRNA 225	225	CGGGCACTCAGACATCATG	1967	CATGATGTCTGAGTGCCCG
siRNA 226	226	GGGCACTCAGACATCATGA	1968	TCATGATGTCTGAGTGCCC
siRNA 227	227	GGCACTCAGACATCATGAG	1969	CTCATGATGTCTGAGTGCC
siRNA 228	228	GCACTCAGACATCATGAGT	1970	ACTCATGATGTCTGAGTGC
siRNA 229	229	CACTCAGACATCATGAGTT	1971	AACTCATGATGTCTGAGTG
siRNA 230	230	ACTCAGACATCATGAGTTG	1972	CAACTCATGATGTCTGAGT
siRNA 231	231	CTCAGACATCATGAGTTGG	1973	CCAACTCATGATGTCTGAG
siRNA 232	232	TCAGACATCATGAGTTGGT	1974	ACCAACTCATGATGTCTGA
siRNA 233	233	CAGACATCATGAGTTGGTC	1975	GACCAACTCATGATGTCTG
siRNA 234	234	AGACATCATGAGTTGGTCC	1976	GGACCAACTCATGATGTCT
siRNA 235	235	GACATCATGAGTTGGTCCT	1977	AGGACCAACTCATGATGTG
siRNA 236	236	ACATCATGAGTTGGTCCTT	1978	AAGGACCAACTCATGATGT
siRNA 237	237	CATCATGAGTTGGTCCTTG	1979	CAAGGACCAACTCATGATG
siRNA 238	238	ATCATGAGTTGGTCCTTGC	1980	GCAAGGACCAACTCATGAT
siRNA 239	239	TCATGAGTTGGTCCTTGCA	1981	TGCAAGGACCAACTCATGA
siRNA 240	240	CATGAGTTGGTCCTTGCA	1982	GTGCAAGGACCAACTCATG
siRNA 241	241	ATGAGTTGGTCCTTGCA	1983	GGTGCAAGGACCAACTCAT
siRNA 242	242	TGAGTTGGTCCTTGCA	1984	GGGTGCAAGGACCAACTCA
siRNA 243	243	GAGTTGGTCCTTGCA	1985	GGGGTGCAAGGACCAACTC
siRNA 244	244	AGTTGGTCCTTGCA	1986	GGGGGTGCAAGGACCAACT
siRNA 245	245	GTTGGTCCTTGCA	1987	CGGGGGTGCAAGGACCAAC
siRNA 246	246	TTGGTCCTTGCA	1988	CCGGGGGTGCAAGGACCAA

siRNA 247	247	TGGTCCTTGCACCCCCGGA	1989	TCCGGGGGTGCAAGGACCA
siRNA 248	248	GGTCCTTGCACCCCCGGAA	1990	TTCCGGGGGTGCAAGGACC
siRNA 249	249	GTCCTTGCACCCCCGGAAT	1991	ATTCCGGGGGTGCAAGGAC
siRNA 250	250	TCCTTGCACCCCCGGAATT	1992	AATTCCGGGGGTGCAAGGA
siRNA 251	251	CCTTGCACCCCCGGAATTT	1993	AAATTCGGGGGTGCAAGG
siRNA 252	252	CTTGCACCCCCGGAATTTA	1994	TAAATTCGGGGGTGCAAG
siRNA 253	253	TTGCACCCCCGGAATTTAA	1995	TTAAATTCGGGGGTGCAA
siRNA 254	254	TGCACCCCCGGAATTTAAT	1996	ATTAAATTCGGGGGTGCA
siRNA 255	255	GCACCCCCGGAATTTAATT	1997	AATTAAATTCGGGGGTGC
siRNA 256	256	CACCCCCGGAATTTAATTC	1998	GAATTAAATTCGGGGGTG
siRNA 257	257	ACCCCCGGAATTTAATTCT	1999	AGAATTAAATTCGGGGGT
siRNA 258	258	CCCCCGGAATTTAATTCTC	2000	GAGAATTAAATTCGGGGG
siRNA 259	259	CCCCCGGAATTTAATTCTCT	2001	AGAGAATTAAATTCGGGG
siRNA 260	260	CCCGGAATTTAATTCTCTA	2002	TAGAGAATTAAATTCGGG
siRNA 261	261	CCGGAATTTAATTCTCTAC	2003	GTAGAGAATTAAATTCGG
siRNA 262	262	CGGAATTTAATTCTCTACT	2004	AGTAGAGAATTAAATTCG
siRNA 263	263	GGAATTTAATTCTCTACTT	2005	AAGTAGAGAATTAAATTC
siRNA 264	264	GAATTTAATTCTCTACTTC	2006	GAAGTAGAGAATTAAATTC
siRNA 265	265	AATTTAATTCTCTACTTCT	2007	AGAAGTAGAGAATTAAATT
siRNA 266	266	ATTTAATTCTCTACTTCTA	2008	TAGAAGTAGAGAATTAAAT
siRNA 267	267	TTTAATTCTCTACTTCTAT	2009	ATAGAAGTAGAGAATTAAA
siRNA 268	268	TTAATTCTCTACTTCTATG	2010	CATAGAAGTAGAGAATTAA
siRNA 269	269	TAATTCTCTACTTCTATGC	2011	GCATAGAAGTAGAGAATTAA
siRNA 270	270	AATTCTCTACTTCTATGCT	2012	AGCATAGAAGTAGAGAATT
siRNA 271	271	ATTCTCTACTTCTATGCTC	2013	GAGCATAGAAGTAGAGAAT
siRNA 272	272	TTCTCTACTTCTATGCTCT	2014	AGAGCATAGAAGTAGAGAA
siRNA 273	273	TCTCTACTTCTATGCTCTT	2015	AAGAGCATAGAAGTAGAGA
siRNA 274	274	CTCTACTTCTATGCTCTTT	2016	AAAGAGCATAGAAGTAGAG
siRNA 275	275	TCTACTTCTATGCTCTTTT	2017	AAAAGAGCATAGAAGTAGA
siRNA 276	276	CTACTTCTATGCTCTTTTA	2018	TAAAAGAGCATAGAAGTAG
siRNA 277	277	TACTTCTATGCTCTTTTAT	2019	ATAAAAAGAGCATAGAAGTA
siRNA 278	278	ACTTCTATGCTCTTTTATT	2020	AATAAAAAGAGCATAGAAGT
siRNA 279	279	CTTCTATGCTCTTTTATTT	2021	AAATAAAAAGAGCATAGAAG
siRNA 280	280	TTCTATGCTCTTTTATTTT	2022	GAAATAAAAAGAGCATAGAA
siRNA 281	281	TCTATGCTCTTTTATTTCT	2023	AGAAATAAAAAGAGCATAGA
siRNA 282	282	CTATGCTCTTTTATTTCTC	2024	GAGAAATAAAAAGAGCATAG
siRNA 283	283	TATGCTCTTTTATTTCTCT	2025	AGAGAAATAAAAAGGCATA
siRNA 284	284	ATGCTCTTTTATTTCTCTC	2026	GAGAGAAATAAAAAGGCAT
siRNA 285	285	TGCTCTTTTATTTCTCTCT	2027	AGAGAGAAATAAAAAGGCA
siRNA 286	286	GCTCTTTTATTTCTCTCTT	2028	AAGAGAGAAATAAAAAGGC
siRNA 287	287	CTCTTTTATTTCTCTCTTC	2029	GAAGAGAGAAATAAAAAGAG
siRNA 288	288	TCTTTTATTTCTCTCTTCA	2030	TGAAGAGAGAAATAAAAAGA
siRNA 289	289	CTTTTATTTCTCTCTTCAA	2031	TTGAAGAGAGAAATAAAAAG
siRNA 290	290	TTTTATTTCTCTCTTCAAC	2032	GTTGAAGAGAGAAATAAAA
siRNA 291	291	TTTATTTCTCTCTTCAACA	2033	TGTTGAAGAGAGAAATAAAA
siRNA 292	292	TTATTTCTCTCTTCAACAT	2034	ATGTTGAAGAGAGAAATAA
siRNA 293	293	TATTTCTCTCTTCAACATG	2035	CATGTTGAAGAGAGAAATA
siRNA 294	294	ATTTCTCTCTTCAACATGT	2036	ACATGTTGAAGAGAGAAAT
siRNA 295	295	TTTCTCTCTTCAACATGTG	2037	CACATGTTGAAGAGAGAAA
siRNA 296	296	TTCTCTCTTCAACATGTGT	2038	ACACATGTTGAAGAGAGAA
siRNA 297	297	TCTCTCTTCAACATGTGTA	2039	TACACATGTTGAAGAGAGA
siRNA 298	298	CTCTCTTCAACATGTGTAG	2040	CTACACATGTTGAAGAGAG

siRNA 299	299	TCTCTTCAACATGTGTAGC	2041	GCTACACATGTTGAAGAGA
siRNA 300	300	CTCTTCAACATGTGTAGCA	2042	TGCTACACATGTTGAAGAG
siRNA 301	301	TCTTCAACATGTGTAGCAT	2043	ATGCTACACATGTTGAAGA
siRNA 302	302	CTTCAACATGTGTAGCATA	2044	TATGCTACACATGTTGAAG
siRNA 303	303	TTCAACATGTGTAGCATAT	2045	ATATGCTACACATGTTGAA
siRNA 304	304	TCAACATGTGTAGCATATG	2046	CATATGCTACACATGTTGA
siRNA 305	305	CAACATGTGTAGCATATGT	2047	ACATATGCTACACATGTTG
siRNA 306	306	AACATGTGTAGCATATGTT	2048	AACATATGCTACACATGTT
siRNA 307	307	ACATGTGTAGCATATGTTG	2049	CAACATATGCTACACATGT
siRNA 308	308	CATGTGTAGCATATGTTGC	2050	GCAACATATGCTACACATG
siRNA 309	309	ATGTGTAGCATATGTTGCT	2051	AGCAACATATGCTACACAT
siRNA 310	310	TGTGTAGCATATGTTGCTA	2052	TAGCAACATATGCTACACA
siRNA 311	311	GTGTAGCATATGTTGCTAC	2053	GTAGCAACATATGCTACAC
siRNA 312	312	TGTAGCATATGTTGCTACC	2054	GGTAGCAACATATGCTACA
siRNA 313	313	GTAGCATATGTTGCTACCA	2055	TGGTAGCAACATATGCTAC
siRNA 314	314	TAGCATATGTTGCTACCAG	2056	CTGGTAGCAACATATGCTA
siRNA 315	315	AGCATATGTTGCTACCAGA	2057	TCTGGTAGCAACATATGCT
siRNA 316	316	GCATATGTTGCTACCAGAG	2058	CTCTGGTAGCAACATATGC
siRNA 317	317	CATATGTTGCTACCAGAGA	2059	TCTCTGGTAGCAACATATG
siRNA 318	318	ATATGTTGCTACCAGAGAC	2060	GTCTCTGGTAGCAACATAT
siRNA 319	319	TATGTTGCTACCAGAGACA	2061	TGTCTCTGGTAGCAACATA
siRNA 320	320	ATGTTGCTACCAGAGACAA	2062	TTGTCTCTGGTAGCAACAT
siRNA 321	321	TGTTGCTACCAGAGACAAC	2063	GTTGTCTCTGGTAGCAACA
siRNA 322	322	GTTGCTACCAGAGACAAC	2064	AGTTGTCTCTGGTAGCAAC
siRNA 323	323	TTGCTACCAGAGACAAC	2065	CAGTTGTCTCTGGTAGCAA
siRNA 324	324	TGCTACCAGAGACAAC	2066	GCAGTTGTCTCTGGTAGCA
siRNA 325	325	GCTACCAGAGACAAC	2067	AGCAGTTGTCTCTGGTAGC
siRNA 326	326	CTACCAGAGACAAC	2068	CAGCAGTTGTCTCTGGTAG
siRNA 327	327	TACCAGAGACAAC	2069	GCAGCAGTTGTCTCTGGTA
siRNA 328	328	ACCAGAGACAAC	2070	TGCAGCAGTTGTCTCTGGT
siRNA 329	329	CCAGAGACAAC	2071	ATGCAGCAGTTGTCTCTGG
siRNA 330	330	CAGAGACAAC	2072	GATGCAGCAGTTGTCTCTG
siRNA 331	331	AGAGACAAC	2073	AGATGCAGCAGTTGTCTCT
siRNA 332	332	GAGACAAC	2074	AAGATGCAGCAGTTGTCTC
siRNA 333	333	AGACAAC	2075	TAAGATGCAGCAGTTGTCT
siRNA 334	334	GACAAC	2076	CTAAGATGCAGCAGTTGTCT
siRNA 335	335	ACAAC	2077	TCTAAGATGCAGCAGTTGT
siRNA 336	336	CAACTGCTGCATCTTAGAT	2078	ATCTAAGATGCAGCAGTTG
siRNA 337	337	AACTGCTGCATCTTAGATG	2079	CATCTAAGATGCAGCAGTT
siRNA 338	338	ACTGCTGCATCTTAGATGA	2080	TCATCTAAGATGCAGCAGT
siRNA 339	339	CTGCTGCATCTTAGATGAA	2081	TTTTCATCTAAGATGCAGCAG
siRNA 340	340	TGCTGCATCTTAGATGAAA	2082	TTTCATCTAAGATGCAGCA
siRNA 341	341	GCTGCATCTTAGATGAAAG	2083	CTTTCATCTAAGATGCAGC
siRNA 342	342	CTGCATCTTAGATGAAAAGA	2084	TCTTTCATCTAAGATGCAG
siRNA 343	343	TGCATCTTAGATGAAAGAT	2085	ATCTTTCATCTAAGATGCA
siRNA 344	344	GCATCTTAGATGAAAGATT	2086	AATCTTTCATCTAAGATGC
siRNA 345	345	CATCTTAGATGAAAGATTTC	2087	GAATCTTTCATCTAAGATG
siRNA 346	346	ATCTTAGATGAAAGATTTCG	2088	CGAATCTTTCATCTAAGAT
siRNA 347	347	TCTTAGATGAAAGATTTCGG	2089	CCGAATCTTTCATCTAAGA
siRNA 348	348	CTTAGATGAAAGATTTCGGT	2090	ACCGAATCTTTCATCTAAG
siRNA 349	349	TTAGATGAAAGATTTCGGTA	2091	TACCGAATCTTTCATCTAA
siRNA 350	350	TAGATGAAAGATTTCGGTAG	2092	CTACCGAATCTTTCATCTA

siRNA 351	351	AGATGAAAGATTCGGTAGT	2093	ACTACCGAATCTTTCATCT
siRNA 352	352	GATGAAAGATTCGGTAGTT	2094	AACACCGAATCTTTCATC
siRNA 353	353	ATGAAAGATTCGGTAGTTA	2095	TAACACCGAATCTTTCAT
siRNA 354	354	TGAAAGATTCGGTAGTTAT	2096	ATAACTACCGAATCTTTC
siRNA 355	355	GAAAGATTCGGTAGTTATT	2097	AATAACTACCGAATCTTTC
siRNA 356	356	AAAGATTCGGTAGTTATTG	2098	CAATAACTACCGAATCTTT
siRNA 357	357	AAGATTCGGTAGTTATTGT	2099	ACAATAACTACCGAATCTT
siRNA 358	358	AGATTCGGTAGTTATTGTC	2100	GACAATAACTACCGAATCT
siRNA 359	359	GATTCGGTAGTTATTGTCC	2101	GGACAATAACTACCGAATC
siRNA 360	360	ATTCGGTAGTTATTGTCCA	2102	TGGACAATAACTACCGAAT
siRNA 361	361	TTCGGTAGTTATTGTCCAA	2103	TTGGACAATAACTACCGAA
siRNA 362	362	TCGGTAGTTATTGTCCAAC	2104	GTTGGACAATAACTACCGA
siRNA 363	363	CGGTAGTTATTGTCCAAC	2105	AGTTGGACAATAACTACCG
siRNA 364	364	GGTAGTTATTGTCCAAC	2106	TAGTTGGACAATAACTACC
siRNA 365	365	GTTAGTTATTGTCCAAC	2107	GTTAGTTGGACAATAACTAC
siRNA 366	366	TAGTTATTGTCCAAC	2108	GGTAGTTGGACAATAACTA
siRNA 367	367	AGTTATTGTCCAAC	2109	AGGTAGTTGGACAATAACT
siRNA 368	368	GTTATTGTCCAAC	2110	CAGGTAGTTGGACAATAAC
siRNA 369	369	TTATTGTCCAAC	2111	ACAGGTAGTTGGACAATAA
siRNA 370	370	TATTGTCCAAC	2112	CACAGGTAGTTGGACAATA
siRNA 371	371	ATTGTCCAAC	2113	CCACAGGTAGTTGGACAAT
siRNA 372	372	TTGTCCAAC	2114	GCCACAGGTAGTTGGACAA
siRNA 373	373	TGTCCAAC	2115	TGCCACAGGTAGTTGGACA
siRNA 374	374	GTCCAAC	2116	ATGCCACAGGTAGTTGGAC
siRNA 375	375	TCCAAC	2117	AATGCCACAGGTAGTTGGA
siRNA 376	376	CCAAC	2118	CAATGCCACAGGTAGTTGG
siRNA 377	377	CAAC	2119	GCAATGCCACAGGTAGTTG
siRNA 378	378	AACTACCTGTGGCATTGCA	2120	TGCAATGCCACAGGTAGTT
siRNA 379	379	ACTACCTGTGGCATTGCAG	2121	CTGCAATGCCACAGGTAGT
siRNA 380	380	CTACCTGTGGCATTGCAGA	2122	TCTGCAATGCCACAGGTAG
siRNA 381	381	TACCTGTGGCATTGCAGAT	2123	ATCTGCAATGCCACAGGTA
siRNA 382	382	ACCTGTGGCATTGCAGATT	2124	AATCTGCAATGCCACAGGT
siRNA 383	383	CCTGTGGCATTGCAGATTT	2125	AAATCTGCAATGCCACAGG
siRNA 384	384	CTGTGGCATTGCAGATTTT	2126	GAAATCTGCAATGCCACAG
siRNA 385	385	TGTGGCATTGCAGATTTCC	2127	GGAAATCTGCAATGCCACA
siRNA 386	386	GTGGCATTGCAGATTTCCCT	2128	AGGAAATCTGCAATGCCAC
siRNA 387	387	TGGCATTGCAGATTTCCCTG	2129	CAGGAAATCTGCAATGCCA
siRNA 388	388	GGCATTGCAGATTTCCCTGT	2130	ACAGGAAATCTGCAATGCC
siRNA 389	389	GCATTGCAGATTTCCCTGTC	2131	GACAGGAAATCTGCAATGTC
siRNA 390	390	CATTGCAGATTTCCCTGTCT	2132	AGACAGGAAATCTGCAATG
siRNA 391	391	ATTGCAGATTTCCCTGTCTA	2133	TAGACAGGAAATCTGCAAT
siRNA 392	392	TTGCAGATTTCCCTGTCTAC	2134	GTAGACAGGAAATCTGCAA
siRNA 393	393	TGCAGATTTCCCTGTCTACT	2135	AGTAGACAGGAAATCTGCA
siRNA 394	394	GCAGATTTCCCTGTCTACTT	2136	AAGTAGACAGGAAATCTGC
siRNA 395	395	CAGATTTCCCTGTCTACTTA	2137	TAAGTAGACAGGAAATCTG
siRNA 396	396	AGATTTCCCTGTCTACTTAT	2138	ATAAGTAGACAGGAAATCT
siRNA 397	397	GATTTCCCTGTCTACTTATC	2139	GATAAGTAGACAGGAAATC
siRNA 398	398	ATTTCCCTGTCTACTTATCA	2140	TGATAAGTAGACAGGAAAT
siRNA 399	399	TTTCCCTGTCTACTTATCAA	2141	TTGATAAGTAGACAGGAAA
siRNA 400	400	TTCCTGTCTACTTATCAAA	2142	TTTGATAAGTAGACAGGAA
siRNA 401	401	TCCTGTCTACTTATCAAAC	2143	GTTTGATAAGTAGACAGGA
siRNA 402	402	CCTGTCTACTTATCAAACC	2144	GGTTTGATAAGTAGACAGG

siRNA 403	403	CTGTCTACTTATCAAACCA	2145	TGGTTTGATAAGTAGACAG
siRNA 404	404	TGTCTACTTATCAAACCAA	2146	TTGGTTTGATAAGTAGACA
siRNA 405	405	GTCTACTTATCAAACCAAA	2147	TTTGGTTTGATAAGTAGAC
siRNA 406	406	TCTACTTATCAAACCAAAG	2148	CTTTGGTTTGATAAGTAGA
siRNA 407	407	CTACTTATCAAACCAAAGT	2149	ACTTTGGTTTGATAAGTAG
siRNA 408	408	TACTTATCAAACCAAAGTA	2150	TACTTTGGTTTGATAAGTA
siRNA 409	409	ACTTATCAAACCAAAGTAG	2151	CTACTTTGGTTTGATAAGT
siRNA 410	410	CTTATCAAACCAAAGTAGA	2152	TCTACTTTGGTTTGATAAG
siRNA 411	411	TTATCAAACCAAAGTAGAC	2153	GTCTACTTTGGTTTGATAA
siRNA 412	412	TATCAAACCAAAGTAGACA	2154	TGTCTACTTTGGTTTGATA
siRNA 413	413	ATCAAACCAAAGTAGACAA	2155	TTGTCTACTTTGGTTTGAT
siRNA 414	414	TCAAACCAAAGTAGACAAG	2156	CTTGTCTACTTTGGTTTGA
siRNA 415	415	CAAACCAAAGTAGACAAGG	2157	CCTTGTCTACTTTGGTTTG
siRNA 416	416	AAACCAAAGTAGACAAGGA	2158	TCCTTGTCTACTTTGGTTT
siRNA 417	417	AACCAAAGTAGACAAGGAT	2159	ATCCTTGTCTACTTTGGTT
siRNA 418	418	ACCAAAGTAGACAAGGATC	2160	GATCCTTGTCTACTTTGGT
siRNA 419	419	CCAAAGTAGACAAGGATCT	2161	AGATCCTTGTCTACTTTGG
siRNA 420	420	CAAAGTAGACAAGGATCTA	2162	TAGATCCTTGTCTACTTTG
siRNA 421	421	AAAGTAGACAAGGATCTAC	2163	GTAGATCCTTGTCTACTTT
siRNA 422	422	AAGTAGACAAGGATCTACA	2164	TGTAGATCCTTGTCTACTT
siRNA 423	423	AGTAGACAAGGATCTACAG	2165	CTGTAGATCCTTGTCTACT
siRNA 424	424	GTAGACAAGGATCTACAGT	2166	ACTGTAGATCCTTGTCTAC
siRNA 425	425	TAGACAAGGATCTACAGTC	2167	GACTGTAGATCCTTGTCTA
siRNA 426	426	AGACAAGGATCTACAGTCT	2168	AGACTGTAGATCCTTGTCT
siRNA 427	427	GACAAGGATCTACAGTCTT	2169	AAGACTGTAGATCCTTGTCT
siRNA 428	428	ACAAGGATCTACAGTCTTT	2170	AAAGACTGTAGATCCTTGT
siRNA 429	429	CAAGGATCTACAGTCTTTG	2171	CAAAGACTGTAGATCCTTG
siRNA 430	430	AAGGATCTACAGTCTTTGG	2172	CCAAAGACTGTAGATCCTT
siRNA 431	431	AGGATCTACAGTCTTTGGA	2173	TCCAAAGACTGTAGATCCT
siRNA 432	432	GGATCTACAGTCTTTGGAA	2174	TTCCAAAGACTGTAGATCC
siRNA 433	433	GATCTACAGTCTTTGGAAG	2175	CTTCCAAAGACTGTAGATC
siRNA 434	434	ATCTACAGTCTTTGGAAGA	2176	TCTTCCAAAGACTGTAGAT
siRNA 435	435	TCTACAGTCTTTGGAAGAC	2177	GTCTTCCAAAGACTGTAGA
siRNA 436	436	CTACAGTCTTTGGAAGACA	2178	TGTCTTCCAAAGACTGTAG
siRNA 437	437	TACAGTCTTTGGAAGACAT	2179	ATGTCTTCCAAAGACTGTA
siRNA 438	438	ACAGTCTTTGGAAGACATC	2180	GATGTCTTCCAAAGACTGT
siRNA 439	439	CAGTCTTTGGAAGACATCT	2181	AGATGTCTTCCAAAGACTG
siRNA 440	440	AGTCTTTGGAAGACATCTT	2182	AAGATGTCTTCCAAAGACT
siRNA 441	441	GTCTTTGGAAGACATCTTA	2183	TAAGATGTCTTCCAAAGAC
siRNA 442	442	TCTTTGGAAGACATCTTAC	2184	GTAAGATGTCTTCCAAAGA
siRNA 443	443	CTTTGGAAGACATCTTACA	2185	TGTAAGATGTCTTCCAAAG
siRNA 444	444	TTTGGAAGACATCTTACAT	2186	ATGTAAGATGTCTTCCAAA
siRNA 445	445	TTGGAAGACATCTTACATC	2187	GATGTAAGATGTCTTCCAA
siRNA 446	446	TGGAAGACATCTTACATCA	2188	TGATGTAAGATGTCTTCCA
siRNA 447	447	GGAAGACATCTTACATCAA	2189	TTGATGTAAGATGTCTTCC
siRNA 448	448	GAAGACATCTTACATCAAG	2190	CTTGATGTAAGATGTCTTC
siRNA 449	449	AAGACATCTTACATCAAGT	2191	ACTTGATGTAAGATGTCTT
siRNA 450	450	AGACATCTTACATCAAGTT	2192	AACTTGATGTAAGATGTCT
siRNA 451	451	GACATCTTACATCAAGTTG	2193	CAACTTGATGTAAGATGTC
siRNA 452	452	ACATCTTACATCAAGTTGA	2194	TCAACTTGATGTAAGATGT
siRNA 453	453	CATCTTACATCAAGTTGAA	2195	TTCAACTTGATGTAAGATG
siRNA 454	454	ATCTTACATCAAGTTGAAA	2196	TTTCAACTTGATGTAAGAT

siRNA 455	455	TCTTACATCAAGTTGAAAA	2197	TTTCAACTTGATGTAAGA
siRNA 456	456	CTTACATCAAGTTGAAAAC	2198	GTTTTCAACTTGATGTAAG
siRNA 457	457	TTACATCAAGTTGAAAACA	2199	TGTTTTCAACTTGATGTAA
siRNA 458	458	TACATCAAGTTGAAAACAA	2200	TTGTTTTCAACTTGATGTA
siRNA 459	459	ACATCAAGTTGAAAACAAA	2201	TTTGTTTTCAACTTGATGT
siRNA 460	460	CATCAAGTTGAAAACAAA	2202	TTTTGTTTTCAACTTGATG
siRNA 461	461	ATCAAGTTGAAAACAAAAC	2203	GTTTTGTTTTCAACTTGAT
siRNA 462	462	TCAAGTTGAAAACAAAACA	2204	TGTTTTGTTTTCAACTTGA
siRNA 463	463	CAAGTTGAAAACAAAACAT	2205	ATGTTTTGTTTTCAACTTG
siRNA 464	464	AAGTTGAAAACAAAACATC	2206	GATGTTTTGTTTTCAACTT
siRNA 465	465	AGTTGAAAACAAAACATCA	2207	TGATGTTTTGTTTTCAACT
siRNA 466	466	GTTGAAAACAAAACATCAG	2208	CTGATGTTTTGTTTTCAAC
siRNA 467	467	TTGAAAACAAAACATCAGA	2209	TCTGATGTTTTGTTTTCAA
siRNA 468	468	TGAAAACAAAACATCAGAA	2210	TTCTGATGTTTTGTTTTCA
siRNA 469	469	GAAAACAAAACATCAGAAG	2211	CTTCTGATGTTTTGTTTTC
siRNA 470	470	AAAACAAAACATCAGAAGT	2212	ACTTCTGATGTTTTGTTTT
siRNA 471	471	AAACAAAACATCAGAAGTC	2213	GACTTCTGATGTTTTGTTT
siRNA 472	472	AACAAAACATCAGAAGTCA	2214	TGACTTCTGATGTTTTGTT
siRNA 473	473	ACAAAACATCAGAAGTCAA	2215	TTGACTTCTGATGTTTTGT
siRNA 474	474	CAAAACATCAGAAGTCAAA	2216	TTTGACTTCTGATGTTTTG
siRNA 475	475	AAAACATCAGAAGTCAAAC	2217	GTTTGACTTCTGATGTTTT
siRNA 476	476	AAACATCAGAAGTCAAACA	2218	TGTTTGACTTCTGATGTTT
siRNA 477	477	AACATCAGAAGTCAAAACAG	2219	CTGTTTGACTTCTGATGTT
siRNA 478	478	ACATCAGAAGTCAAAACAGC	2220	GCTGTTTGACTTCTGATGT
siRNA 479	479	CATCAGAAGTCAAAACAGCT	2221	AGCTGTTTGACTTCTGATG
siRNA 480	480	ATCAGAAGTCAAAACAGCTG	2222	CAGCTGTTTGACTTCTGAT
siRNA 481	481	TCAGAAGTCAAAACAGCTGA	2223	TCAGCTGTTTGACTTCTGA
siRNA 482	482	CAGAAGTCAAAACAGCTGAT	2224	ATCAGCTGTTTGACTTCTG
siRNA 483	483	AGAAGTCAAAACAGCTGATA	2225	TATCAGCTGTTTGACTTCT
siRNA 484	484	GAAGTCAAAACAGCTGATAA	2226	TTATCAGCTGTTTGACTTC
siRNA 485	485	AAGTCAAAACAGCTGATAAA	2227	TTTATCAGCTGTTTGACTT
siRNA 486	486	AGTCAAAACAGCTGATAAAA	2228	TTTTATCAGCTGTTTGACT
siRNA 487	487	GTCAAAACAGCTGATAAAAG	2229	CTTTTATCAGCTGTTTGAC
siRNA 488	488	TCAAACAGCTGATAAAAGC	2230	GCTTTTATCAGCTGTTTGA
siRNA 489	489	CAAACAGCTGATAAAAGCA	2231	TGCTTTTATCAGCTGTTTG
siRNA 490	490	AAACAGCTGATAAAAGCAA	2232	TTGCTTTTATCAGCTGTTT
siRNA 491	491	AACAGCTGATAAAAGCAAT	2233	ATTGCTTTTATCAGCTGTT
siRNA 492	492	ACAGCTGATAAAAGCAATC	2234	GATTGCTTTTATCAGCTGT
siRNA 493	493	CAGCTGATAAAAGCAATCC	2235	GGATTGCTTTTATCAGCTG
siRNA 494	494	AGCTGATAAAAGCAATCCA	2236	TGGATTGCTTTTATCAGCT
siRNA 495	495	GCTGATAAAAGCAATCCAA	2237	TTGGATTGCTTTTATCAGC
siRNA 496	496	CTGATAAAAGCAATCCAAC	2238	GTTGGATTGCTTTTATCAG
siRNA 497	497	TGATAAAAGCAATCCAAC	2239	AGTTGGATTGCTTTTATCA
siRNA 498	498	GATAAAAGCAATCCAAC	2240	GAGTTGGATTGCTTTTATC
siRNA 499	499	ATAAAAGCAATCCAAC	2241	TGAGTTGGATTGCTTTTAT
siRNA 500	500	TAAAAGCAATCCAAC	2242	GTGAGTTGGATTGCTTTTA
siRNA 501	501	AAAAGCAATCCAAC	2243	AGTGAGTTGGATTGCTTTT
siRNA 502	502	AAAGCAATCCAAC	2244	AAGTGAGTTGGATTGCTTT
siRNA 503	503	AAGCAATCCAAC	2245	TAAGTGAGTTGGATTGCTT
siRNA 504	504	AGCAATCCAAC	2246	ATAAGTGAGTTGGATTGCT
siRNA 505	505	GCAATCCAAC	2247	TATAAGTGAGTTGGATTGC
siRNA 506	506	CAATCCAAC	2248	TTATAAGTGAGTTGGATTG

siRNA 507	507	AATCCAACCTCACTTATAAT	2249	ATTATAAGTGAGTTGGATT
siRNA 508	508	ATCCAACCTCACTTATAATC	2250	GATTATAAGTGAGTTGGAT
siRNA 509	509	TCCAACCTCACTTATAATCC	2251	GGATTATAAGTGAGTTGGA
siRNA 510	510	CCAACCTCACTTATAATCCT	2252	AGGATTATAAGTGAGTTGG
siRNA 511	511	CAACCTCACTTATAATCCTG	2253	CAGGATTATAAGTGAGTTG
siRNA 512	512	AACTCACTTATAATCCTGA	2254	TCAGGATTATAAGTGAGTT
siRNA 513	513	ACTCACTTATAATCCTGAT	2255	ATCAGGATTATAAGTGAGT
siRNA 514	514	CTCACTTATAATCCTGATG	2256	CATCAGGATTATAAGTGAG
siRNA 515	515	TCACTTATAATCCTGATGA	2257	TCATCAGGATTATAAGTGA
siRNA 516	516	CACTTATAATCCTGATGAA	2258	TTCATCAGGATTATAAGTG
siRNA 517	517	ACTTATAATCCTGATGAAT	2259	ATTCATCAGGATTATAAGT
siRNA 518	518	CTTATAATCCTGATGAATC	2260	GATTCATCAGGATTATAAG
siRNA 519	519	TTATAATCCTGATGAATCA	2261	TGATTCATCAGGATTATAA
siRNA 520	520	TATAATCCTGATGAATCAT	2262	ATGATTCATCAGGATTATA
siRNA 521	521	ATAATCCTGATGAATCATC	2263	GATGATTCATCAGGATTAT
siRNA 522	522	TAATCCTGATGAATCATCA	2264	TGATGATTCATCAGGATTA
siRNA 523	523	AATCCTGATGAATCATCAA	2265	TTGATGATTCATCAGGATT
siRNA 524	524	ATCCTGATGAATCATCAAA	2266	TTTGATGATTCATCAGGAT
siRNA 525	525	TCCTGATGAATCATCAAAA	2267	TTTTGATGATTCATCAGGA
siRNA 526	526	CCTGATGAATCATCAAAAC	2268	GTTTTGATGATTCATCAGG
siRNA 527	527	CTGATGAATCATCAAAACC	2269	GGTTTTGATGATTCATCAG
siRNA 528	528	TGATGAATCATCAAAACCA	2270	TGGTTTTGATGATTCATCA
siRNA 529	529	GATGAATCATCAAAACCAA	2271	TTGGTTTTGATGATTCATC
siRNA 530	530	ATGAATCATCAAAACCAAA	2272	TTTGGTTTTGATGATTCAT
siRNA 531	531	TGAATCATCAAAACCAAAT	2273	ATTTGGTTTTGATGATTCA
siRNA 532	532	GAATCATCAAAACCAAATA	2274	TATTTGGTTTTGATGATTG
siRNA 533	533	AATCATCAAAACCAAATAT	2275	ATATTTGGTTTTGATGATT
siRNA 534	534	ATCATCAAAACCAAATATG	2276	CATATTTGGTTTTGATGAT
siRNA 535	535	TCATCAAAACCAAATATGA	2277	TCATATTTGGTTTTGATGA
siRNA 536	536	CATCAAAACCAAATATGAT	2278	ATCATATTTGGTTTTGATG
siRNA 537	537	ATCAAAACCAAATATGATA	2279	TATCATATTTGGTTTTGAT
siRNA 538	538	TCAAAACCAAATATGATAG	2280	CTATCATATTTGGTTTTGA
siRNA 539	539	CAAAACCAAATATGATAGA	2281	TCTATCATATTTGGTTTTG
siRNA 540	540	AAAACCAAATATGATAGAC	2282	GTCTATCATATTTGGTTTT
siRNA 541	541	AAACCAAATATGATAGACG	2283	CGTCTATCATATTTGGTTT
siRNA 542	542	AACCAAATATGATAGACGC	2284	GCGTCTATCATATTTGGTT
siRNA 543	543	ACCAAATATGATAGACGCT	2285	AGCGTCTATCATATTTGGT
siRNA 544	544	CCAAATATGATAGACGCTG	2286	CAGCGTCTATCATATTTGG
siRNA 545	545	CAAATATGATAGACGCTGC	2287	GCAGCGTCTATCATATTTG
siRNA 546	546	AAATATGATAGACGCTGCT	2288	AGCAGCGTCTATCATATTT
siRNA 547	547	AATATGATAGACGCTGCTA	2289	TAGCAGCGTCTATCATATT
siRNA 548	548	ATATGATAGACGCTGCTAC	2290	GTAGCAGCGTCTATCATAT
siRNA 549	549	TATGATAGACGCTGCTACT	2291	AGTAGCAGCGTCTATCATA
siRNA 550	550	ATGATAGACGCTGCTACTT	2292	AAGTAGCAGCGTCTATCAT
siRNA 551	551	TGATAGACGCTGCTACTTT	2293	AAAGTAGCAGCGTCTATCA
siRNA 552	552	GATAGACGCTGCTACTTTG	2294	CAAAGTAGCAGCGTCTATC
siRNA 553	553	ATAGACGCTGCTACTTTGA	2295	TCAAAGTAGCAGCGTCTAT
siRNA 554	554	TAGACGCTGCTACTTTGAA	2296	TTCAAAGTAGCAGCGTCTA
siRNA 555	555	AGACGCTGCTACTTTGAAG	2297	CTTCAAAGTAGCAGCGTCT
siRNA 556	556	GACGCTGCTACTTTGAAGT	2298	ACTTCAAAGTAGCAGCGTC
siRNA 557	557	ACGCTGCTACTTTGAAGTC	2299	GACTTCAAAGTAGCAGCGT
siRNA 558	558	CGCTGCTACTTTGAAGTCC	2300	GGACTTCAAAGTAGCAGCG

siRNA 559	559	GCTGCTACTTTGAAGTCCA	2301	TGGACTTCAAAGTAGCAGC
siRNA 560	560	CTGCTACTTTGAAGTCCAG	2302	CTGGACTTCAAAGTAGCAG
siRNA 561	561	TGCTACTTTGAAGTCCAGG	2303	CCTGGACTTCAAAGTAGCA
siRNA 562	562	GCTACTTTGAAGTCCAGGA	2304	TCCTGGACTTCAAAGTAGC
siRNA 563	563	CTACTTTGAAGTCCAGGAA	2305	TTCTGGACTTCAAAGTAG
siRNA 564	564	TACTTTGAAGTCCAGGAAA	2306	TTCTGGACTTCAAAGTA
siRNA 565	565	ACTTTGAAGTCCAGGAAAA	2307	TTTCTGGACTTCAAAGT
siRNA 566	566	CTTTGAAGTCCAGGAAAAT	2308	ATTTCTGGACTTCAAAG
siRNA 567	567	TTTGAAGTCCAGGAAAATG	2309	CATTTCTGGACTTCAA
siRNA 568	568	TTGAAGTCCAGGAAAATGT	2310	ACATTTCTGGACTTCAA
siRNA 569	569	TGAAGTCCAGGAAAATGTT	2311	AACATTTCTGGACTTCA
siRNA 570	570	GAAGTCCAGGAAAATGTTA	2312	TAACATTTCTGGACTTC
siRNA 571	571	AAGTCCAGGAAAATGTTAG	2313	CTAACATTTCTGGACTT
siRNA 572	572	AGTCCAGGAAAATGTTAGA	2314	TCTAACATTTCTGGACT
siRNA 573	573	GTCCAGGAAAATGTTAGAA	2315	TTCTAACATTTCTGGAC
siRNA 574	574	TCCAGGAAAATGTTAGAAG	2316	CTTCTAACATTTCTGGG
siRNA 575	575	CCAGGAAAATGTTAGAAGA	2317	TCTTCTAACATTTCTGG
siRNA 576	576	CAGGAAAATGTTAGAAGAA	2318	TTCTTCTAACATTTCTG
siRNA 577	577	AGGAAAATGTTAGAAGAAA	2319	TTTCTTCTAACATTTCT
siRNA 578	578	GGAAAATGTTAGAAGAAAT	2320	ATTTCTTCTAACATTTCC
siRNA 579	579	GAAAATGTTAGAAGAAATT	2321	AATTTCTTCTAACATTTT
siRNA 580	580	AAAATGTTAGAAGAAATTA	2322	TAATTTCTTCTAACATTT
siRNA 581	581	AAATGTTAGAAGAAATTAT	2323	ATAATTTCTTCTAACATT
siRNA 582	582	AATGTTAGAAGAAATTATG	2324	CATAATTTCTTCTAACATT
siRNA 583	583	ATGTTAGAAGAAATTATGA	2325	TCATAATTTCTTCTAACAT
siRNA 584	584	TGTTAGAAGAAATTATGAA	2326	TTCATAATTTCTTCTAACA
siRNA 585	585	GTTAGAAGAAATTATGAAA	2327	TTTCATAATTTCTTCTAAC
siRNA 586	586	TTAGAAGAAATTATGAAAT	2328	ATTTTCATAATTTCTTCTAA
siRNA 587	587	TAGAAGAAATTATGAAATA	2329	TATTTTCATAATTTCTTCTA
siRNA 588	588	AGAAGAAATTATGAAATAT	2330	ATATTTTCATAATTTCTTCT
siRNA 589	589	GAAGAAATTATGAAATATG	2331	CATATTTTCATAATTTCTTC
siRNA 590	590	AAGAAATTATGAAATATGA	2332	TCATATTTTCATAATTTCTT
siRNA 591	591	AGAAATTATGAAATATGAA	2333	TTCATATTTTCATAATTTCT
siRNA 592	592	GAAATTATGAAATATGAAG	2334	CTTCATATTTTCATAATTTCT
siRNA 593	593	AAATTATGAAATATGAAGC	2335	GCTTCATATTTTCATAATTT
siRNA 594	594	AATTATGAAATATGAAGCA	2336	TGCTTCATATTTTCATAATT
siRNA 595	595	ATTATGAAATATGAAGCAT	2337	ATGCTTCATATTTTCATAAT
siRNA 596	596	TTATGAAATATGAAGCATC	2338	GATGCTTCATATTTTCATAA
siRNA 597	597	TATGAAATATGAAGCATCG	2339	CGATGCTTCATATTTTCATA
siRNA 598	598	ATGAAATATGAAGCATCGA	2340	TCGATGCTTCATATTTTCAT
siRNA 599	599	TGAAATATGAAGCATCGAT	2341	ATCGATGCTTCATATTTTCA
siRNA 600	600	GAAATATGAAGCATCGATT	2342	AATCGATGCTTCATATTTT
siRNA 601	601	AAATATGAAGCATCGATTT	2343	AAATCGATGCTTCATATTT
siRNA 602	602	AATATGAAGCATCGATTTT	2344	AAAATCGATGCTTCATATT
siRNA 603	603	ATATGAAGCATCGATTTTA	2345	TAAAATCGATGCTTCATAT
siRNA 604	604	TATGAAGCATCGATTTTAA	2346	TTAAAATCGATGCTTCATA
siRNA 605	605	ATGAAGCATCGATTTTAAC	2347	GTAAAATCGATGCTTCAT
siRNA 606	606	TGAAGCATCGATTTTAACA	2348	TGTTAAAATCGATGCTTCA
siRNA 607	607	GAAGCATCGATTTTAACAC	2349	GTGTTAAAATCGATGCTTC
siRNA 608	608	AAGCATCGATTTTAACACA	2350	TGTGTTAAAATCGATGCTT
siRNA 609	609	AGCATCGATTTTAACACAT	2351	ATGTGTTAAAATCGATGCT
siRNA 610	610	GCATCGATTTTAACACATG	2352	CATGTGTTAAAATCGATGC

siRNA 611	611	CATCGATTTTAAACACATGA	2353	TCATGTGTGTTAAAAATCGATG
siRNA 612	612	ATCGATTTTAAACACATGAC	2354	GTCATGTGTGTTAAAAATCGAT
siRNA 613	613	TCGATTTTAAACACATGACT	2355	AGTCATGTGTGTTAAAAATCGA
siRNA 614	614	CGATTTTAAACACATGACTC	2356	GAGTCATGTGTGTTAAAAATCG
siRNA 615	615	GATTTTAAACACATGACTCA	2357	TGAGTCATGTGTGTTAAAAATC
siRNA 616	616	ATTTTAAACACATGACTCAA	2358	TTGAGTCATGTGTGTTAAAAAT
siRNA 617	617	TTTTAACACATGACTCAAG	2359	CTTGAGTCATGTGTGTTAAAA
siRNA 618	618	TTTAACACATGACTCAAGT	2360	ACTTGAGTCATGTGTGTTAAA
siRNA 619	619	TTAACACATGACTCAAGTA	2361	TACTTGAGTCATGTGTGTTAA
siRNA 620	620	TAACACATGACTCAAGTAT	2362	ATACTTGAGTCATGTGTGTTA
siRNA 621	621	AACACATGACTCAAGTATT	2363	AATACTTGAGTCATGTGTGTT
siRNA 622	622	ACACATGACTCAAGTATTC	2364	GAATACTTGAGTCATGTGTG
siRNA 623	623	CACATGACTCAAGTATTCG	2365	CGAATACTTGAGTCATGTGTG
siRNA 624	624	ACATGACTCAAGTATTCGA	2366	TCGAATACTTGAGTCATGTGT
siRNA 625	625	CATGACTCAAGTATTCGAT	2367	ATCGAATACTTGAGTCATGTG
siRNA 626	626	ATGACTCAAGTATTCGATA	2368	TATCGAATACTTGAGTCATGT
siRNA 627	627	TGACTCAAGTATTCGATAT	2369	ATATCGAATACTTGAGTCATG
siRNA 628	628	GACTCAAGTATTCGATATT	2370	AATATCGAATACTTGAGTCAT
siRNA 629	629	ACTCAAGTATTCGATATTT	2371	AAATATCGAATACTTGAGTC
siRNA 630	630	CTCAAGTATTCGATATTTG	2372	CAAATATCGAATACTTGAGTC
siRNA 631	631	TCAAGTATTCGATATTTGC	2373	GCAAATATCGAATACTTGAG
siRNA 632	632	CAAGTATTCGATATTTGCA	2374	TGCAAATATCGAATACTTGAG
siRNA 633	633	AAGTATTCGATATTTGCAG	2375	CTGCAAATATCGAATACTTG
siRNA 634	634	AGTATTCGATATTTGCAGG	2376	CCTGCAAATATCGAATACTTG
siRNA 635	635	GTATTCGATATTTGCAGGA	2377	TCCTGCAAATATCGAATACTG
siRNA 636	636	TATTCGATATTTGCAGGAA	2378	TTCTGCAAATATCGAATACTG
siRNA 637	637	ATTCGATATTTGCAGGAAA	2379	TTTCTGCAAATATCGAATACT
siRNA 638	638	TTCGATATTTGCAGGAAAT	2380	ATTTCTGCAAATATCGAATACT
siRNA 639	639	TCGATATTTGCAGGAAATA	2381	TATTTCTGCAAATATCGAATA
siRNA 640	640	CGATATTTGCAGGAAATAT	2382	ATATTTCTGCAAATATCGAATA
siRNA 641	641	GATATTTGCAGGAAATATA	2383	TATATTTCTGCAAATATCGAATA
siRNA 642	642	ATATTTGCAGGAAATATAT	2384	ATATATTTCTGCAAATATCGAATA
siRNA 643	643	TATTTGCAGGAAATATATA	2385	TATATATTTCTGCAAATATCGAATA
siRNA 644	644	ATTTGCAGGAAATATATAA	2386	TTATATATTTCTGCAAATATCGAATA
siRNA 645	645	TTTGCAGGAAATATATAAT	2387	ATTATATATTTCTGCAAATATCGAATA
siRNA 646	646	TTGCAGGAAATATATAATT	2388	AATTATATATTTCTGCAAATATCGAATA
siRNA 647	647	TGCAGGAAATATATAATTTC	2389	GAATTATATATTTCTGCAAATATCGAATA
siRNA 648	648	GCAGGAAATATATAATTCA	2390	TGAATTATATATTTCTGCAAATATCGAATA
siRNA 649	649	CAGGAAATATATAATTCAA	2391	TTGAATTATATATTTCTGCAAATATCGAATA
siRNA 650	650	AGGAAATATATAATTCAAA	2392	TTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 651	651	GGAAATATATAATTCAAAT	2393	ATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 652	652	GAAATATATAATTCAAATA	2394	TATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 653	653	AAATATATAATTCAAATAA	2395	TTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 654	654	AATATATAATTCAAATAAT	2396	ATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 655	655	ATATATAATTCAAATAATC	2397	GATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 656	656	TATATAATTCAAATAATCA	2398	TGATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 657	657	ATATAATTCAAATAATCAA	2399	TTGATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 658	658	TATAATTCAAATAATCAAA	2400	TTTGATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 659	659	ATAATTCAAATAATCAAAA	2401	TTTTGATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 660	660	TAATTCAAATAATCAAAAAG	2402	CTTTTGATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 661	661	AATTCAAATAATCAAAAAGA	2403	TCTTTTGATTATTTGAATTATATATTTCTGCAAATATCGAATA
siRNA 662	662	ATTCAAATAATCAAAAAGAT	2404	ATCTTTTGATTATTTGAATTATATATTTCTGCAAATATCGAATA

siRNA 663	663	TTCAAATAATCAAAAGATT	2405	AATCTTTTGATTATTTGAA
siRNA 664	664	TCAAATAATCAAAAGATTG	2406	CAATCTTTTGATTATTTGA
siRNA 665	665	CAAATAATCAAAAGATTGT	2407	ACAATCTTTTGATTATTTG
siRNA 666	666	AAATAATCAAAAGATTGTT	2408	AACAATCTTTTGATTATTT
siRNA 667	667	AATAATCAAAAGATTGTTA	2409	TAACAATCTTTTGATTATT
siRNA 668	668	ATAATCAAAAGATTGTAA	2410	TTAACAATCTTTTGATTAT
siRNA 669	669	TAATCAAAAGATTGTAAAC	2411	GTTAACAATCTTTTGATT
siRNA 670	670	AATCAAAAGATTGTAAACC	2412	GGTTAACAATCTTTTGATT
siRNA 671	671	ATCAAAAGATTGTAAACCT	2413	AGGTTAACAATCTTTTGAT
siRNA 672	672	TCAAAAGATTGTAAACCTG	2414	CAGGTTAACAATCTTTTGA
siRNA 673	673	CAAAAGATTGTAAACCTGA	2415	TCAGGTTAACAATCTTTTG
siRNA 674	674	AAAAGATTGTAAACCTGAA	2416	TTCAGGTTAACAATCTTTT
siRNA 675	675	AAAGATTGTAAACCTGAAA	2417	TTTCAGGTTAACAATCTTT
siRNA 676	676	AAGATTGTAAACCTGAAAG	2418	CTTTCAGGTTAACAATCTT
siRNA 677	677	AGATTGTAAACCTGAAAGA	2419	TCTTTCAGGTTAACAATCT
siRNA 678	678	GATTGTAAACCTGAAAGAG	2420	CTCTTTCAGGTTAACAATC
siRNA 679	679	ATTGTAAACCTGAAAGAGA	2421	TCTCTTTCAGGTTAACAAT
siRNA 680	680	TTGTAAACCTGAAAGAGAA	2422	TTCTCTTTCAGGTTAACAA
siRNA 681	681	TGTAAACCTGAAAGAGAAG	2423	CTTCTCTTTCAGGTTAACA
siRNA 682	682	GTTAACCTGAAAGAGAAGG	2424	CCTTCTCTTTCAGGTTAAC
siRNA 683	683	TTAACCTGAAAGAGAAGGT	2425	ACCTTCTCTTTCAGGTAA
siRNA 684	684	TAACCTGAAAGAGAAGGTA	2426	TACCTTCTCTTTCAGGTTA
siRNA 685	685	AACCTGAAAGAGAAGGTAG	2427	CTACCTTCTCTTTCAGGTT
siRNA 686	686	ACCTGAAAGAGAAGGTAGC	2428	GCTACCTTCTCTTTCAGGT
siRNA 687	687	CCTGAAAGAGAAGGTAGCC	2429	GGCTACCTTCTCTTTCAGG
siRNA 688	688	CTGAAAGAGAAGGTAGCCC	2430	GGGCTACCTTCTCTTTCAG
siRNA 689	689	TGAAAGAGAAGGTAGCCCA	2431	TGGGCTACCTTCTCTTTCA
siRNA 690	690	GAAAGAGAAGGTAGCCCAG	2432	CTGGGCTACCTTCTCTTTC
siRNA 691	691	AAAGAGAAGGTAGCCCAGC	2433	GCTGGGCTACCTTCTCTTT
siRNA 692	692	AAGAGAAGGTAGCCCAGCT	2434	AGCTGGGCTACCTTCTCTT
siRNA 693	693	AGAGAAGGTAGCCCAGCTT	2435	AAGCTGGGCTACCTTCTCT
siRNA 694	694	GAGAAGGTAGCCCAGCTTG	2436	CAAGCTGGGCTACCTTCTC
siRNA 695	695	AGAAGGTAGCCCAGCTTGA	2437	TCAAGCTGGGCTACCTTCT
siRNA 696	696	GAAGGTAGCCCAGCTTGAA	2438	TTCAAGCTGGGCTACCTTC
siRNA 697	697	AAGGTAGCCCAGCTTGAAG	2439	CTTCAAGCTGGGCTACCTT
siRNA 698	698	AGGTAGCCCAGCTTGAAGC	2440	GCTTCAAGCTGGGCTACCT
siRNA 699	699	GGTAGCCCAGCTTGAAGCA	2441	TGCTTCAAGCTGGGCTACC
siRNA 700	700	GTAGCCCAGCTTGAAGCAC	2442	GTGCTTCAAGCTGGGCTAC
siRNA 701	701	TAGCCCAGCTTGAAGCAC	2443	TGTGCTTCAAGCTGGGCTA
siRNA 702	702	AGCCCAGCTTGAAGCACAG	2444	CTGTGCTTCAAGCTGGGCT
siRNA 703	703	GCCCAGCTTGAAGCACAGT	2445	ACTGTGCTTCAAGCTGGGC
siRNA 704	704	CCCAGCTTGAAGCACAGTG	2446	CACTGTGCTTCAAGCTGGG
siRNA 705	705	CCAGCTTGAAGCACAGTGC	2447	GCACTGTGCTTCAAGCTGG
siRNA 706	706	CAGCTTGAAGCACAGTGCC	2448	GGCACTGTGCTTCAAGCTG
siRNA 707	707	AGCTTGAAGCACAGTGCCA	2449	TGGCACTGTGCTTCAAGCT
siRNA 708	708	GCTTGAAGCACAGTGCCAG	2450	CTGGCACTGTGCTTCAAGC
siRNA 709	709	CTTGAAGCACAGTGCCAGG	2451	CCTGGCACTGTGCTTCAAG
siRNA 710	710	TTGAAGCACAGTGCCAGGA	2452	TCCTGGCACTGTGCTTCAA
siRNA 711	711	TGAAGCACAGTGCCAGGAA	2453	TTCTGGCACTGTGCTTCA
siRNA 712	712	GAAGCACAGTGCCAGGAAC	2454	GTTCTGGCACTGTGCTTC
siRNA 713	713	AAGCACAGTGCCAGGAACC	2455	GGTTCCTGGCACTGTGCTT
siRNA 714	714	AGCACAGTGCCAGGAACCT	2456	AGGTTCTGGCACTGTGCT

siRNA 715	715	GCACAGTGCCAGGAACCTT	2457	AAGGTTCCCTGGCACTGTGC
siRNA 716	716	CACAGTGCCAGGAACCTTG	2458	CAAGGTTCCCTGGCACTGTG
siRNA 717	717	ACAGTGCCAGGAACCTTGC	2459	GCAAGGTTCCCTGGCACTGT
siRNA 718	718	CAGTGCCAGGAACCTTGCA	2460	TGCAAGGTTCCCTGGCACTG
siRNA 719	719	AGTGCCAGGAACCTTGCAA	2461	TTGCAAGGTTCCCTGGCACT
siRNA 720	720	GTGCCAGGAACCTTGCAAA	2462	TTTGCAAGGTTCCCTGGCAC
siRNA 721	721	TGCCAGGAACCTTGCAAAG	2463	CTTTGCAAGGTTCCCTGGCA
siRNA 722	722	GCCAGGAACCTTGCAAAGA	2464	TCTTTGCAAGGTTCCCTGGC
siRNA 723	723	CCAGGAACCTTGCAAAGAC	2465	GTCTTTGCAAGGTTCCCTGG
siRNA 724	724	CAGGAACCTTGCAAAGACA	2466	TGTCTTTGCAAGGTTCCCTG
siRNA 725	725	AGGAACCTTGCAAAGACAC	2467	GTGTCTTTGCAAGGTTCCCT
siRNA 726	726	GGAACCTTGCAAAGACACG	2468	CGTGTCTTTGCAAGGTTCC
siRNA 727	727	GAACCTTGCAAAGACACGG	2469	CCGTGTCTTTGCAAGGTTTC
siRNA 728	728	AACCTTGCAAAGACACGGT	2470	ACCGTGTCTTTGCAAGGTT
siRNA 729	729	ACCTTGCAAAGACACGGTG	2471	CACCGTGTCTTTGCAAGGT
siRNA 730	730	CCTTGCAAAGACACGGTGC	2472	GCACCGTGTCTTTGCAAGG
siRNA 731	731	CTTGCAAAGACACGGTGCA	2473	TGCACCGTGTCTTTGCAAG
siRNA 732	732	TTGCAAAGACACGGTGCAA	2474	TTGCACCGTGTCTTTGCAA
siRNA 733	733	TGCAAAGACACGGTGCAAA	2475	TTTGCACCGTGTCTTTGCA
siRNA 734	734	GCAAAGACACGGTGCAAAT	2476	ATTTGCACCGTGTCTTTGC
siRNA 735	735	CAAAGACACGGTGCAAATC	2477	GATTTGCACCGTGTCTTTG
siRNA 736	736	AAAGACACGGTGCAAATCC	2478	GGATTTGCACCGTGTCTTT
siRNA 737	737	AAGACACGGTGCAAATCCA	2479	TGGATTTGCACCGTGTCTT
siRNA 738	738	AGACACGGTGCAAATCCAT	2480	ATGGATTTGCACCGTGTCT
siRNA 739	739	GACACGGTGCAAATCCATG	2481	CATGGATTTGCACCGTGTCT
siRNA 740	740	ACACGGTGCAAATCCATGA	2482	TCATGGATTTGCACCGTGT
siRNA 741	741	CACGGTGCAAATCCATGAT	2483	ATCATGGATTTGCACCGTGT
siRNA 742	742	ACGGTGCAAATCCATGATA	2484	TATCATGGATTTGCACCGT
siRNA 743	743	CGGTGCAAATCCATGATAT	2485	ATATCATGGATTTGCACCG
siRNA 744	744	GGTGCAAATCCATGATATC	2486	GATATCATGGATTTGCACC
siRNA 745	745	GTGCAAATCCATGATATCA	2487	TGATATCATGGATTTGCAC
siRNA 746	746	TGCAAATCCATGATATCAC	2488	GTGATATCATGGATTTGCA
siRNA 747	747	GCAAATCCATGATATCACT	2489	AGTGATATCATGGATTTGC
siRNA 748	748	CAAATCCATGATATCACTG	2490	CAGTGATATCATGGATTTG
siRNA 749	749	AAATCCATGATATCACTGG	2491	CCAGTGATATCATGGATTT
siRNA 750	750	AATCCATGATATCACTGGG	2492	CCCAGTGATATCATGGATT
siRNA 751	751	ATCCATGATATCACTGGGA	2493	TCCCAGTGATATCATGGAT
siRNA 752	752	TCCATGATATCACTGGGAA	2494	TTCCCAGTGATATCATGGAA
siRNA 753	753	CCATGATATCACTGGGAAA	2495	TTTCCCAGTGATATCATGG
siRNA 754	754	CATGATATCACTGGGAAAG	2496	CTTTCCCAGTGATATCATG
siRNA 755	755	ATGATATCACTGGGAAAGA	2497	TCTTTCCCAGTGATATCAT
siRNA 756	756	TGATATCACTGGGAAAGAT	2498	ATCTTTCCCAGTGATATCA
siRNA 757	757	GATATCACTGGGAAAGATT	2499	AATCTTTCCCAGTGATATC
siRNA 758	758	ATATCACTGGGAAAGATTG	2500	CAATCTTTCCCAGTGATAT
siRNA 759	759	TATCACTGGGAAAGATTGT	2501	ACAATCTTTCCCAGTGATA
siRNA 760	760	ATCACTGGGAAAGATTGTC	2502	GACAATCTTTCCCAGTGAT
siRNA 761	761	TCACTGGGAAAGATTGTCA	2503	TGACAATCTTTCCCAGTGA
siRNA 762	762	CACTGGGAAAGATTGTCAA	2504	TTGACAATCTTTCCCAGTG
siRNA 763	763	ACTGGGAAAGATTGTCAAG	2505	CTTGACAATCTTTCCCAGT
siRNA 764	764	CTGGGAAAGATTGTCAAGA	2506	TCTTGACAATCTTTCCCAG
siRNA 765	765	TGGGAAAGATTGTCAAGAC	2507	GTCTTGACAATCTTTCCCA
siRNA 766	766	GGGAAAGATTGTCAAGACA	2508	TGTCTTGACAATCTTTCCC

siRNA 767	767	GGAAAGATTGTCAAGACAT	2509	ATGTCTTGACAATCTTTCC
siRNA 768	768	GAAAGATTGTCAAGACATT	2510	AATGTCTTGACAATCTTTC
siRNA 769	769	AAAGATTGTCAAGACATTG	2511	CAATGTCTTGACAATCTTT
siRNA 770	770	AAGATTGTCAAGACATTGC	2512	GCAATGTCTTGACAATCTT
siRNA 771	771	AGATTGTCAAGACATTGCC	2513	GGCAATGTCTTGACAATCT
siRNA 772	772	GATTGTCAAGACATTGCCA	2514	TGGCAATGTCTTGACAATC
siRNA 773	773	ATTGTCAAGACATTGCCAA	2515	TTGGCAATGTCTTGACAAT
siRNA 774	774	TTGTCAAGACATTGCCAAT	2516	ATTGGCAATGTCTTGACAA
siRNA 775	775	TGTCAAGACATTGCCAATA	2517	TATTGGCAATGTCTTGACA
siRNA 776	776	GTCAAGACATTGCCAATAA	2518	TTATTGGCAATGTCTTGAC
siRNA 777	777	TCAAGACATTGCCAATAAG	2519	CTTATTGGCAATGTCTTGA
siRNA 778	778	CAAGACATTGCCAATAAGG	2520	CCTTATTGGCAATGTCTTG
siRNA 779	779	AAGACATTGCCAATAAGGG	2521	CCCTTATTGGCAATGTCTT
siRNA 780	780	AGACATTGCCAATAAGGGA	2522	TCCCTTATTGGCAATGTCT
siRNA 781	781	GACATTGCCAATAAGGGAG	2523	CTCCCTTATTGGCAATGTC
siRNA 782	782	ACATTGCCAATAAGGGAGC	2524	GCTCCCTTATTGGCAATGT
siRNA 783	783	CATTGCCAATAAGGGAGCT	2525	AGCTCCCTTATTGGCAATG
siRNA 784	784	ATTGCCAATAAGGGAGCTA	2526	TAGCTCCCTTATTGGCAAT
siRNA 785	785	TTGCCAATAAGGGAGCTAA	2527	TTAGCTCCCTTATTGGCAA
siRNA 786	786	TGCCAATAAGGGAGCTAAA	2528	TTTAGCTCCCTTATTGGCA
siRNA 787	787	GCCAATAAGGGAGCTAAAC	2529	GTTTAGCTCCCTTATTGGC
siRNA 788	788	CCAATAAGGGAGCTAAACA	2530	TGTTTAGCTCCCTTATTGG
siRNA 789	789	CAATAAGGGAGCTAAACAG	2531	CTGTTTAGCTCCCTTATTG
siRNA 790	790	AATAAGGGAGCTAAACAGA	2532	TCTGTTTAGCTCCCTTATT
siRNA 791	791	ATAAGGGAGCTAAACAGAG	2533	CTCTGTTTAGCTCCCTTAT
siRNA 792	792	TAAGGGAGCTAAACAGAGC	2534	GCTCTGTTTAGCTCCCTTA
siRNA 793	793	AAGGGAGCTAAACAGAGCG	2535	CGCTCTGTTTAGCTCCCTT
siRNA 794	794	AGGGAGCTAAACAGAGCGG	2536	CCGCTCTGTTTAGCTCCCT
siRNA 795	795	GGGAGCTAAACAGAGCGGG	2537	CCCGCTCTGTTTAGCTCCC
siRNA 796	796	GGAGCTAAACAGAGCGGGC	2538	GCCCGCTCTGTTTAGCTCC
siRNA 797	797	GAGCTAAACAGAGCGGGCT	2539	AGCCCGCTCTGTTTAGCTC
siRNA 798	798	AGCTAAACAGAGCGGGCTT	2540	AAGCCCGCTCTGTTTAGCT
siRNA 799	799	GCTAAACAGAGCGGGCTTT	2541	AAAGCCCGCTCTGTTTAGC
siRNA 800	800	CTAAACAGAGCGGGCTTTA	2542	TAAAGCCCGCTCTGTTTAG
siRNA 801	801	TAAACAGAGCGGGCTTTAC	2543	GTAAAGCCCGCTCTGTTTA
siRNA 802	802	AAACAGAGCGGGCTTTACT	2544	AGTAAAGCCCGCTCTGTTT
siRNA 803	803	AACAGAGCGGGCTTTACTT	2545	AAGTAAAGCCCGCTCTGTT
siRNA 804	804	ACAGAGCGGGCTTTACTTT	2546	AAAGTAAAGCCCGCTCTGT
siRNA 805	805	CAGAGCGGGCTTTACTTTA	2547	TAAAGTAAAGCCCGCTCTG
siRNA 806	806	AGAGCGGGCTTTACTTTAT	2548	ATAAGTAAAGCCCGCTCT
siRNA 807	807	GAGCGGGCTTTACTTTATT	2549	AATAAGTAAAGCCCGCTC
siRNA 808	808	AGCGGGCTTTACTTTATTAT	2550	TAATAAGTAAAGCCCGCT
siRNA 809	809	GCGGGCTTTACTTTATTAA	2551	TTAATAAGTAAAGCCCGC
siRNA 810	810	CGGGCTTTACTTTATTAAA	2552	TTTAATAAGTAAAGCCCG
siRNA 811	811	GGGCTTTACTTTATTAAAC	2553	GTTTAATAAGTAAAGCCC
siRNA 812	812	GGCTTTACTTTATTAAACC	2554	GGTTTAATAAGTAAAGCC
siRNA 813	813	GCTTTACTTTATTAAACCT	2555	AGGTTTAATAAGTAAAGC
siRNA 814	814	CTTTACTTTATTAAACCTC	2556	GAGGTTTAATAAGTAAAG
siRNA 815	815	TTTACTTTATTAAACCTCT	2557	AGAGGTTTAATAAGTAAA
siRNA 816	816	TTACTTTATTAAACCTCTG	2558	CAGAGGTTTAATAAGTAA
siRNA 817	817	TACTTTATTAAACCTCTGA	2559	TCAGAGGTTTAATAAGTA
siRNA 818	818	ACTTTATTAAACCTCTGAA	2560	TTCAGAGGTTTAATAAGT

siRNA 819	819	CTTTATTAAACCTCTGAAA	2561	TTTCAGAGGTTTAATAAAG
siRNA 820	820	TTTATTAAACCTCTGAAAG	2562	CTTTCAGAGGTTTAATAAA
siRNA 821	821	TTATTAAACCTCTGAAAGC	2563	GCTTTCAGAGGTTTAATAA
siRNA 822	822	TATTAAACCTCTGAAAGCT	2564	AGCTTTCAGAGGTTTAATA
siRNA 823	823	ATTAAACCTCTGAAAGCTA	2565	TAGCTTTCAGAGGTTTAAT
siRNA 824	824	TTAAACCTCTGAAAGCTAA	2566	TTAGCTTTCAGAGGTTTAA
siRNA 825	825	TAAACCTCTGAAAGCTAAC	2567	GTTAGCTTTCAGAGGTTTA
siRNA 826	826	AAACCTCTGAAAGCTAACC	2568	GGTTAGCTTTCAGAGGTTT
siRNA 827	827	AACCTCTGAAAGCTAACCA	2569	TGGTTAGCTTTCAGAGGTT
siRNA 828	828	ACCTCTGAAAGCTAACCAG	2570	CTGGTTAGCTTTCAGAGGT
siRNA 829	829	CCTCTGAAAGCTAACCAGC	2571	GCTGGTTAGCTTTCAGAGG
siRNA 830	830	CTCTGAAAGCTAACCAGCA	2572	TGCTGGTTAGCTTTCAGAG
siRNA 831	831	TCTGAAAGCTAACCAGCAA	2573	TTGCTGGTTAGCTTTCAGA
siRNA 832	832	CTGAAAGCTAACCAGCAAT	2574	ATTGCTGGTTAGCTTTCAG
siRNA 833	833	TGAAAGCTAACCAGCAATT	2575	AATTGCTGGTTAGCTTTC
siRNA 834	834	GAAAGCTAACCAGCAATTC	2576	GAATTGCTGGTTAGCTTTC
siRNA 835	835	AAAGCTAACCAGCAATTCT	2577	AGAATTGCTGGTTAGCTTT
siRNA 836	836	AAGCTAACCAGCAATTCTT	2578	AAGAATTGCTGGTTAGCTT
siRNA 837	837	AGCTAACCAGCAATTCTTA	2579	TAAGAATTGCTGGTTAGCT
siRNA 838	838	GCTAACCAGCAATTCTTAG	2580	CTAAGAATTGCTGGTTAGC
siRNA 839	839	CTAACCAGCAATTCTTAGT	2581	ACTAAGAATTGCTGGTTAG
siRNA 840	840	TAACCAGCAATTCTTAGTC	2582	GACTAAGAATTGCTGGTTA
siRNA 841	841	AACCAGCAATTCTTAGTCT	2583	AGACTAAGAATTGCTGGTT
siRNA 842	842	ACCAGCAATTCTTAGTCTA	2584	TAGACTAAGAATTGCTGGT
siRNA 843	843	CCAGCAATTCTTAGTCTAC	2585	GTAGACTAAGAATTGCTGG
siRNA 844	844	CAGCAATTCTTAGTCTACT	2586	AGTAGACTAAGAATTGCTG
siRNA 845	845	AGCAATTCTTAGTCTACTG	2587	CAGTAGACTAAGAATTGCT
siRNA 846	846	GCAATTCTTAGTCTACTGT	2588	ACAGTAGACTAAGAATTGC
siRNA 847	847	CAATTCTTAGTCTACTGTG	2589	CACAGTAGACTAAGAATTG
siRNA 848	848	AATTCTTAGTCTACTGTGA	2590	TCACAGTAGACTAAGAATT
siRNA 849	849	ATTCTTAGTCTACTGTGAA	2591	TTACAGTAGACTAAGAAT
siRNA 850	850	TTCTTAGTCTACTGTGAAA	2592	TTTACAGTAGACTAAGAA
siRNA 851	851	TCTTAGTCTACTGTGAAAT	2593	ATTTACAGTAGACTAAGA
siRNA 852	852	CTTAGTCTACTGTGAAATC	2594	GATTTACAGTAGACTAAG
siRNA 853	853	TTAGTCTACTGTGAAATCG	2595	CGATTTACAGTAGACTAA
siRNA 854	854	TAGTCTACTGTGAAATCGA	2596	TCGATTTACAGTAGACTA
siRNA 855	855	AGTCTACTGTGAAATCGAT	2597	ATCGATTTACAGTAGACT
siRNA 856	856	GTCTACTGTGAAATCGATG	2598	CATCGATTTACAGTAGAC
siRNA 857	857	TCTACTGTGAAATCGATGG	2599	CCATCGATTTACAGTAGA
siRNA 858	858	CTACTGTGAAATCGATGGG	2600	CCCATCGATTTACAGTAG
siRNA 859	859	TACTGTGAAATCGATGGGT	2601	ACCCATCGATTTACAGTA
siRNA 860	860	ACTGTGAAATCGATGGGTC	2602	GACCCATCGATTTACAGT
siRNA 861	861	CTGTGAAATCGATGGGTCT	2603	AGACCCATCGATTTACAG
siRNA 862	862	TGTGAAATCGATGGGTCTG	2604	CAGACCCATCGATTTACA
siRNA 863	863	GTGAAATCGATGGGTCTGG	2605	CCAGACCCATCGATTTAC
siRNA 864	864	TGAAATCGATGGGTCTGGA	2606	TCCAGACCCATCGATTTCA
siRNA 865	865	GAAATCGATGGGTCTGGAA	2607	TTCCAGACCCATCGATTT
siRNA 866	866	AAATCGATGGGTCTGGAAA	2608	TTTCCAGACCCATCGATT
siRNA 867	867	AATCGATGGGTCTGGAAAT	2609	ATTTCCAGACCCATCGATT
siRNA 868	868	ATCGATGGGTCTGGAAATG	2610	CATTTCCAGACCCATCGAT
siRNA 869	869	TCGATGGGTCTGGAAATGG	2611	CCATTTCCAGACCCATCGA
siRNA 870	870	CGATGGGTCTGGAAATGGA	2612	TCCATTTCCAGACCCATCG

siRNA 871	871	GATGGGTCTGGAAATGGAT	2613	ATCCATTTCCAGACCCATC
siRNA 872	872	ATGGGTCTGGAAATGGATG	2614	CATCCATTTCCAGACCCAT
siRNA 873	873	TGGGTCTGGAAATGGATGG	2615	CCATCCATTTCCAGACCCA
siRNA 874	874	GGGTCTGGAAATGGATGGA	2616	TCCATCCATTTCCAGACCC
siRNA 875	875	GGTCTGGAAATGGATGGAC	2617	GTCCATCCATTTCCAGACC
siRNA 876	876	GTCTGGAAATGGATGGACT	2618	AGTCCATCCATTTCCAGAC
siRNA 877	877	TCTGGAAATGGATGGACTG	2619	CAGTCCATCCATTTCCAGA
siRNA 878	878	CTGGAAATGGATGGACTGT	2620	ACAGTCCATCCATTTCCAG
siRNA 879	879	TGGAAATGGATGGACTGTG	2621	CACAGTCCATCCATTTCCA
siRNA 880	880	GGAAATGGATGGACTGTGT	2622	ACACAGTCCATCCATTTCC
siRNA 881	881	GAAATGGATGGACTGTGTT	2623	AACACAGTCCATCCATTTT
siRNA 882	882	AAATGGATGGACTGTGTTT	2624	AAACACAGTCCATCCATTT
siRNA 883	883	AATGGATGGACTGTGTTTC	2625	GAAACACAGTCCATCCATT
siRNA 884	884	ATGGATGGACTGTGTTTCA	2626	TGAAACACAGTCCATCCAT
siRNA 885	885	TGGATGGACTGTGTTTCAG	2627	CTGAAACACAGTCCATCCA
siRNA 886	886	GGATGGACTGTGTTTCAGA	2628	TCTGAAACACAGTCCATCC
siRNA 887	887	GATGGACTGTGTTTCAGAA	2629	TTCTGAAACACAGTCCATC
siRNA 888	888	ATGGACTGTGTTTCAGAAG	2630	CTTCTGAAACACAGTCCAT
siRNA 889	889	TGGACTGTGTTTCAGAAGA	2631	TCTTCTGAAACACAGTCCA
siRNA 890	890	GGACTGTGTTTCAGAAGAG	2632	CTCTTCTGAAACACAGTCC
siRNA 891	891	GACTGTGTTTCAGAAGAGA	2633	TCTCTTCTGAAACACAGTC
siRNA 892	892	ACTGTGTTTCAGAAGAGAC	2634	GTCTCTTCTGAAACACAGT
siRNA 893	893	CTGTGTTTCAGAAGAGACT	2635	AGTCTCTTCTGAAACACAG
siRNA 894	894	TGTGTTTCAGAAGAGACTT	2636	AAGTCTCTTCTGAAACACA
siRNA 895	895	GTGTTTCAGAAGAGACTTG	2637	CAAGTCTCTTCTGAAACAC
siRNA 896	896	TGTTTCAGAAGAGACTTGA	2638	TCAAGTCTCTTCTGAAACA
siRNA 897	897	GTTTCAGAAGAGACTTGAT	2639	ATCAAGTCTCTTCTGAAAC
siRNA 898	898	TTTCAGAAGAGACTTGATG	2640	CATCAAGTCTCTTCTGAAA
siRNA 899	899	TTCAGAAGAGACTTGATGG	2641	CCATCAAGTCTCTTCTGAA
siRNA 900	900	TCAGAAGAGACTTGATGGC	2642	GCCATCAAGTCTCTTCTGA
siRNA 901	901	CAGAAGAGACTTGATGGCA	2643	TGCCATCAAGTCTCTTCTG
siRNA 902	902	AGAAGAGACTTGATGGCAG	2644	CTGCCATCAAGTCTCTTCT
siRNA 903	903	GAAGAGACTTGATGGCAGT	2645	ACTGCCATCAAGTCTCTTC
siRNA 904	904	AAGAGACTTGATGGCAGTG	2646	CACTGCCATCAAGTCTCTT
siRNA 905	905	AGAGACTTGATGGCAGTGT	2647	ACACTGCCATCAAGTCTCT
siRNA 906	906	GAGACTTGATGGCAGTGTA	2648	TACACTGCCATCAAGTCTC
siRNA 907	907	AGACTTGATGGCAGTGTAG	2649	CTACACTGCCATCAAGTCT
siRNA 908	908	GACTTGATGGCAGTGTAGA	2650	TCTACACTGCCATCAAGTC
siRNA 909	909	ACTTGATGGCAGTGTAGAT	2651	ATCTACACTGCCATCAAGT
siRNA 910	910	CTTGATGGCAGTGTAGATT	2652	AATCTACACTGCCATCAAG
siRNA 911	911	TTGATGGCAGTGTAGATTT	2653	AAATCTACACTGCCATCAA
siRNA 912	912	TGATGGCAGTGTAGATTTT	2654	GAAATCTACACTGCCATCA
siRNA 913	913	GATGGCAGTGTAGATTTTCA	2655	TGAAATCTACACTGCCATC
siRNA 914	914	ATGGCAGTGTAGATTTTCAA	2656	TTGAAATCTACACTGCCAT
siRNA 915	915	TGGCAGTGTAGATTTTCAAG	2657	CTTGAAATCTACACTGCCA
siRNA 916	916	GGCAGTGTAGATTTTCAAGA	2658	TCTTGAAATCTACACTGCC
siRNA 917	917	GCAGTGTAGATTTTCAAGAA	2659	TTCTTGAAATCTACACTGC
siRNA 918	918	CAGTGTAGATTTTCAAGAAA	2660	TTTCTTGAAATCTACACTG
siRNA 919	919	AGTGTAGATTTTCAAGAAAA	2661	TTTTCTTGAAATCTACACT
siRNA 920	920	GTGTAGATTTTCAAGAAAAA	2662	TTTTTCTTGAAATCTACAC
siRNA 921	921	TGTAGATTTTCAAGAAAAAC	2663	GTTTTTCTTGAAATCTACA
siRNA 922	922	GTAGATTTTCAAGAAAAACT	2664	AGTTTTTCTTGAAATCTAC

siRNA 923	923	TAGATTTCAAGAAAACTG	2665	CAGTTTTTCTTGAAATCTA
siRNA 924	924	AGATTTCAAGAAAACTGG	2666	CCAGTTTTTCTTGAAATCT
siRNA 925	925	GATTTCAAGAAAACTGGA	2667	TCCAGTTTTTCTTGAAATC
siRNA 926	926	ATTTCAAGAAAACTGGAT	2668	ATCCAGTTTTTCTTGAAAT
siRNA 927	927	TTTCAAGAAAACTGGATT	2669	AATCCAGTTTTTCTTGAAA
siRNA 928	928	TTCAAGAAAACTGGATT	2670	GAATCCAGTTTTTCTTGAA
siRNA 929	929	TCAAGAAAACTGGATTCA	2671	TGAATCCAGTTTTTCTTG
siRNA 930	930	CAAGAAAACTGGATTCAA	2672	TTGAATCCAGTTTTTCTTG
siRNA 931	931	AAGAAAACTGGATTCAAT	2673	ATTGAATCCAGTTTTTCTT
siRNA 932	932	AGAAAACTGGATTCAATA	2674	TATTGAATCCAGTTTTTCT
siRNA 933	933	GAAAACTGGATTCAATAT	2675	ATATTGAATCCAGTTTTTC
siRNA 934	934	AAAACTGGATTCAATATA	2676	TATATTGAATCCAGTTTTT
siRNA 935	935	AAACTGGATTCAATATAA	2677	TTATATTGAATCCAGTTTT
siRNA 936	936	AACTGGATTCAATATAAA	2678	TTTATATTGAATCCAGTTT
siRNA 937	937	AACTGGATTCAATATAAAG	2679	CTTTATATTGAATCCAGTT
siRNA 938	938	ACTGGATTCAATATAAAGA	2680	TCTTTATATTGAATCCAGT
siRNA 939	939	CTGGATTCAATATAAAGAA	2681	TTCTTTATATTGAATCCAG
siRNA 940	940	TGGATTCAATATAAAGAAG	2682	CTTCTTTATATTGAATCCA
siRNA 941	941	GGATTCAATATAAAGAAGG	2683	CCTTCTTTATATTGAATCC
siRNA 942	942	GATTCAATATAAAGAAGGA	2684	TCCTTCTTTATATTGAATC
siRNA 943	943	ATTCAATATAAAGAAGGAT	2685	ATCCTTCTTTATATTGAAT
siRNA 944	944	TCAATATAAAGAAGGATT	2686	AATCCTTCTTTATATTGAA
siRNA 945	945	TCAATATAAAGAAGGATTT	2687	AAATCCTTCTTTATATTGA
siRNA 946	946	CAATATAAAGAAGGATTTG	2688	CAAATCCTTCTTTATATTG
siRNA 947	947	AATATAAAGAAGGATTTGG	2689	CCAAATCCTTCTTTATATT
siRNA 948	948	ATATAAAGAAGGATTTGGA	2690	TCCAAATCCTTCTTTATAT
siRNA 949	949	TATAAAGAAGGATTTGGAC	2691	GTCCAAATCCTTCTTTATA
siRNA 950	950	ATAAAGAAGGATTTGGACA	2692	TGTCCAAATCCTTCTTTAT
siRNA 951	951	TAAAGAAGGATTTGGACAT	2693	ATGTCCAAATCCTTCTTTA
siRNA 952	952	AAAGAAGGATTTGGACATC	2694	GATGTCCAAATCCTTCTTT
siRNA 953	953	AAGAAGGATTTGGACATCT	2695	AGATGTCCAAATCCTTCTT
siRNA 954	954	AGAAGGATTTGGACATCTG	2696	CAGATGTCCAAATCCTTCT
siRNA 955	955	GAAGGATTTGGACATCTGT	2697	ACAGATGTCCAAATCCTTC
siRNA 956	956	AAGGATTTGGACATCTGTC	2698	GACAGATGTCCAAATCCTT
siRNA 957	957	AGGATTTGGACATCTGTCT	2699	AGACAGATGTCCAAATCCT
siRNA 958	958	GGATTTGGACATCTGTCTC	2700	GAGACAGATGTCCAAATCC
siRNA 959	959	GATTTGGACATCTGTCTCC	2701	GGAGACAGATGTCCAAATC
siRNA 960	960	ATTTGGACATCTGTCTCCT	2702	AGGAGACAGATGTCCAAAT
siRNA 961	961	TTTGGACATCTGTCTCCTA	2703	TAGGAGACAGATGTCCAAA
siRNA 962	962	TTGGACATCTGTCTCCTAC	2704	GTAGGAGACAGATGTCCAA
siRNA 963	963	TGGACATCTGTCTCCTACT	2705	AGTAGGAGACAGATGTCCA
siRNA 964	964	GGACATCTGTCTCCTACTG	2706	CAGTAGGAGACAGATGTCC
siRNA 965	965	GACATCTGTCTCCTACTGG	2707	CCAGTAGGAGACAGATGTC
siRNA 966	966	ACATCTGTCTCCTACTGGC	2708	GCCAGTAGGAGACAGATGT
siRNA 967	967	CATCTGTCTCCTACTGGCA	2709	TGCCAGTAGGAGACAGATG
siRNA 968	968	ATCTGTCTCCTACTGGCAC	2710	GTGCCAGTAGGAGACAGAT
siRNA 969	969	TCTGTCTCCTACTGGCACA	2711	TGTGCCAGTAGGAGACAGA
siRNA 970	970	CTGTCTCCTACTGGCACAA	2712	TTGTGCCAGTAGGAGACAG
siRNA 971	971	TGTCTCCTACTGGCACAA	2713	GTTGTGCCAGTAGGAGACA
siRNA 972	972	GTCTCCTACTGGCACAA	2714	TGTTGTGCCAGTAGGAGAC
siRNA 973	973	TCTCCTACTGGCACAA	2715	CTGTTGTGCCAGTAGGAGA
siRNA 974	974	CTCCTACTGGCACAA	2716	TCTGTTGTGCCAGTAGGAG

siRNA 975	975	TCCTACTGGCACAACAGAA	2717	TTCTGTTGTGCCAGTAGGA
siRNA 976	976	CCTACTGGCACAACAGAAT	2718	ATTCTGTTGTGCCAGTAGG
siRNA 977	977	CTACTGGCACAACAGAATT	2719	AATTCTGTTGTGCCAGTAG
siRNA 978	978	TACTGGCACAACAGAATTT	2720	AAATTCTGTTGTGCCAGTA
siRNA 979	979	ACTGGCACAACAGAATTTT	2721	AAAATTCTGTTGTGCCAGT
siRNA 980	980	CTGGCACAACAGAATTTTG	2722	CAAAATTCTGTTGTGCCAG
siRNA 981	981	TGGCACAACAGAATTTTGG	2723	CCAAAATTCTGTTGTGCCA
siRNA 982	982	GGCACAACAGAATTTTGGC	2724	GCCAAAATTCTGTTGTGCC
siRNA 983	983	GCACAACAGAATTTTGGCT	2725	AGCCAAAATTCTGTTGTGC
siRNA 984	984	CACAACAGAATTTTGGCTG	2726	CAGCCAAAATTCTGTTGTG
siRNA 985	985	ACAACAGAATTTTGGCTGG	2727	CCAGCCAAAATTCTGTTGT
siRNA 986	986	CAACAGAATTTTGGCTGGG	2728	CCCAGCCAAAATTCTGTTG
siRNA 987	987	AACAGAATTTTGGCTGGGA	2729	TCCCAGCCAAAATTCTGTT
siRNA 988	988	ACAGAATTTTGGCTGGGAA	2730	TTCCCAGCCAAAATTCTGT
siRNA 989	989	CAGAATTTTGGCTGGGAAA	2731	TTTCCCAGCCAAAATTCTG
siRNA 990	990	AGAATTTTGGCTGGGAAAT	2732	ATTTCCCAGCCAAAATTCT
siRNA 991	991	GAATTTTGGCTGGGAAATG	2733	CATTTCCCAGCCAAAATTC
siRNA 992	992	AATTTTGGCTGGGAAATGA	2734	TCATTTCCCAGCCAAAATT
siRNA 993	993	ATTTTGGCTGGGAAATGAG	2735	CTCATTTCCCAGCCAAAAT
siRNA 994	994	TTTTGGCTGGGAAATGAGA	2736	TCTCATTTCCCAGCCAAAA
siRNA 995	995	TTTGGCTGGGAAATGAGAA	2737	TTCTCATTTCCCAGCCAAA
siRNA 996	996	TTGGCTGGGAAATGAGAAAG	2738	CTTCTCATTTCCCAGCCAA
siRNA 997	997	TGGCTGGGAAATGAGAAAG	2739	TCTTCTCATTTCCCAGCCA
siRNA 998	998	GGCTGGGAAATGAGAAAGAT	2740	ATCTTCTCATTTCCCAGCC
siRNA 999	999	GCTGGGAAATGAGAAAGATT	2741	AATCTTCTCATTTCCCAGC
siRNA 1000	1000	CTGGGAAATGAGAAAGATTC	2742	GAATCTTCTCATTTCCCAG
siRNA 1001	1001	TGGGAAATGAGAAAGATTCA	2743	TGAATCTTCTCATTTCCCA
siRNA 1002	1002	GGGAAATGAGAAAGATTTCAT	2744	ATGAATCTTCTCATTTCCC
siRNA 1003	1003	GGAAATGAGAAAGATTTCATT	2745	AATGAATCTTCTCATTTCC
siRNA 1004	1004	GAAATGAGAAAGATTTCATTT	2746	AAATGAATCTTCTCATTTT
siRNA 1005	1005	AAATGAGAAAGATTTCATTTG	2747	CAAATGAATCTTCTCATTT
siRNA 1006	1006	AATGAGAAAGATTTCATTTGA	2748	TCAAATGAATCTTCTCATTT
siRNA 1007	1007	ATGAGAAAGATTTCATTTGAT	2749	ATCAAATGAATCTTCTCAT
siRNA 1008	1008	TGAGAAAGATTTCATTTGATA	2750	TATCAAATGAATCTTCTCA
siRNA 1009	1009	GAGAAAGATTTCATTTGATAA	2751	TTATCAAATGAATCTTCTC
siRNA 1010	1010	AGAAGATTTCATTTGATAAG	2752	CTTATCAAATGAATCTTCT
siRNA 1011	1011	GAAGATTTCATTTGATAAGC	2753	GCTTATCAAATGAATCTTC
siRNA 1012	1012	AAGATTTCATTTGATAAGCA	2754	TGCTTATCAAATGAATCTT
siRNA 1013	1013	AGATTTCATTTGATAAGCAC	2755	GTGCTTATCAAATGAATCT
siRNA 1014	1014	GATTTCATTTGATAAGCACAC	2756	TGTGCTTATCAAATGAATC
siRNA 1015	1015	ATTCATTTGATAAGCACAC	2757	GTGTGCTTATCAAATGAAT
siRNA 1016	1016	TTCATTTGATAAGCACACACA	2758	TGTGTGCTTATCAAATGAA
siRNA 1017	1017	TCATTTGATAAGCACACACAG	2759	CTGTGTGCTTATCAAATGA
siRNA 1018	1018	CATTTGATAAGCACACACAGT	2760	ACTGTGTGCTTATCAAATG
siRNA 1019	1019	ATTTGATAAGCACACACAGTC	2761	GACTGTGTGCTTATCAAAT
siRNA 1020	1020	TTTGATAAGCACACAGTCT	2762	AGACTGTGTGCTTATCAAA
siRNA 1021	1021	TTGATAAGCACACAGTCTG	2763	CAGACTGTGTGCTTATCAA
siRNA 1022	1022	TGATAAGCACACAGTCTGCG	2764	GCAGACTGTGTGCTTATCA
siRNA 1023	1023	GATAAGCACACAGTCTGCC	2765	GGCAGACTGTGTGCTTATC
siRNA 1024	1024	ATAAGCACACAGTCTGCCA	2766	TGGCAGACTGTGTGCTTAT
siRNA 1025	1025	TAAGCACACAGTCTGCCAT	2767	ATGGCAGACTGTGTGCTTA
siRNA 1026	1026	AAGCACACAGTCTGCCATC	2768	GATGGCAGACTGTGTGCTT

siRNA 1027	1027	AGCACACAGTCTGCCATCC	2769	GGATGGCAGACTGTGTGCT
siRNA 1028	1028	GCACACAGTCTGCCATCCC	2770	GGGATGGCAGACTGTGTGC
siRNA 1029	1029	CACACAGTCTGCCATCCCA	2771	TGGGATGGCAGACTGTGTG
siRNA 1030	1030	ACACAGTCTGCCATCCCAT	2772	ATGGGATGGCAGACTGTGT
siRNA 1031	1031	CACAGTCTGCCATCCCAT	2773	TATGGGATGGCAGACTGTG
siRNA 1032	1032	ACAGTCTGCCATCCCATAT	2774	ATATGGGATGGCAGACTGT
siRNA 1033	1033	CAGTCTGCCATCCCATATG	2775	CATATGGGATGGCAGACTG
siRNA 1034	1034	AGTCTGCCATCCCATATGC	2776	GCATATGGGATGGCAGACT
siRNA 1035	1035	GTCTGCCATCCCATATGCA	2777	TGCATATGGGATGGCAGAC
siRNA 1036	1036	TCTGCCATCCCATATGCAT	2778	ATGCATATGGGATGGCAGA
siRNA 1037	1037	CTGCCATCCCATATGCATT	2779	AATGCATATGGGATGGCAG
siRNA 1038	1038	TGCCATCCCATATGCATTA	2780	TAATGCATATGGGATGGCA
siRNA 1039	1039	GCCATCCCATATGCATTAA	2781	TTAATGCATATGGGATGGC
siRNA 1040	1040	CCATCCCATATGCATTAAAG	2782	CTTAATGCATATGGGATGG
siRNA 1041	1041	CATCCCATATGCATTAAAGA	2783	TCTTAATGCATATGGGATG
siRNA 1042	1042	ATCCCATATGCATTAAAGAG	2784	CTCTTAATGCATATGGGAT
siRNA 1043	1043	TCCCATATGCATTAAAGAGT	2785	ACTCTTAATGCATATGGGA
siRNA 1044	1044	CCCATATGCATTAAAGAGTG	2786	CACTCTTAATGCATATGGG
siRNA 1045	1045	CCATATGCATTAAAGAGTGG	2787	CCACTCTTAATGCATATGG
siRNA 1046	1046	CATATGCATTAAAGAGTGGA	2788	TCCACTCTTAATGCATATG
siRNA 1047	1047	ATATGCATTAAAGAGTGGA	2789	TTCCACTCTTAATGCATAT
siRNA 1048	1048	TATGCATTAAAGAGTGGAAC	2790	GTTCCACTCTTAATGCATA
siRNA 1049	1049	ATGCATTAAAGAGTGGAAC	2791	AGTTCCACTCTTAATGCAT
siRNA 1050	1050	TGCATTAAAGAGTGGAAC	2792	CAGTTCCACTCTTAATGCA
siRNA 1051	1051	GCATTAAAGAGTGGAAC	2793	CCAGTTCCACTCTTAATGC
siRNA 1052	1052	CATTAAAGAGTGGAAC	2794	TCCAGTTCCACTCTTAATG
siRNA 1053	1053	ATTAAGAGTGGAAC	2795	TTCCAGTTCCACTCTTAAT
siRNA 1054	1054	TTAAGAGTGGAAC	2796	CTTCCAGTTCCACTCTTAA
siRNA 1055	1055	TAAGAGTGGAAC	2797	TCTTCCAGTTCCACTCTTA
siRNA 1056	1056	AAGAGTGGAAC	2798	GTCTTCCAGTTCCACTCTT
siRNA 1057	1057	AGAGTGGAAC	2799	AGTCTTCCAGTTCCACTCT
siRNA 1058	1058	GAGTGGAAC	2800	CAGTCTTCCAGTTCCACTC
siRNA 1059	1059	AGTGGAAC	2801	CCAGTCTTCCAGTTCCACT
siRNA 1060	1060	GTGGAAC	2802	TCCAGTCTTCCAGTTCCAC
siRNA 1061	1061	TGGAAC	2803	TTCCAGTCTTCCAGTTCCA
siRNA 1062	1062	GGAAC	2804	ATTCCAGTCTTCCAGTTCC
siRNA 1063	1063	GAAC	2805	CATTCCAGTCTTCCAGTTC
siRNA 1064	1064	AAC	2806	CCATTCCAGTCTTCCAGTT
siRNA 1065	1065	ACTGGAAGACTGGAATGGC	2807	GCCATTCCAGTCTTCCAGT
siRNA 1066	1066	CTGGAAGACTGGAATGGCA	2808	TGCCATTCCAGTCTTCCAG
siRNA 1067	1067	TGGAAGACTGGAATGGCAG	2809	CTGCCATTCCAGTCTTCCA
siRNA 1068	1068	GGAAGACTGGAATGGCAGA	2810	TCTGCCATTCCAGTCTTCC
siRNA 1069	1069	GAAGACTGGAATGGCAGAA	2811	TTCTGCCATTCCAGTCTTC
siRNA 1070	1070	AAGACTGGAATGGCAGAAC	2812	GTTCTGCCATTCCAGTCTT
siRNA 1071	1071	AGACTGGAATGGCAGAAC	2813	GGTCTGCCATTCCAGTCT
siRNA 1072	1072	GACTGGAATGGCAGAACCA	2814	TGGTTCTGCCATTCCAGTC
siRNA 1073	1073	ACTGGAATGGCAGAACCA	2815	CTGGTTCTGCCATTCCAGT
siRNA 1074	1074	CTGGAATGGCAGAACCA	2816	ACTGGTTCTGCCATTCCAG
siRNA 1075	1075	TGGAATGGCAGAACCA	2817	TACTGGTTCTGCCATTCCA
siRNA 1076	1076	GGAATGGCAGAACCA	2818	GTAAGTTCTGCCATTCC
siRNA 1077	1077	GAATGGCAGAACCA	2819	AGTAAGTTCTGCCATTCC
siRNA 1078	1078	AATGGCAGAACCA	2820	CAGTAAGTTCTGCCATT

siRNA 1079	1079	ATGGCAGAACCAGTACTGC	2821	GCAGTACTGGTTCTGCCAT
siRNA 1080	1080	TGGCAGAACCAGTACTGCA	2822	TGCAGTACTGGTTCTGCCA
siRNA 1081	1081	GGCAGAACCAGTACTGCAG	2823	CTGCAGTACTGGTTCTGCC
siRNA 1082	1082	GCAGAACCAGTACTGCAGA	2824	TCTGCAGTACTGGTTCTGC
siRNA 1083	1083	CAGAACCAGTACTGCAGAC	2825	GTCTGCAGTACTGGTTCTG
siRNA 1084	1084	AGAACCAGTACTGCAGACT	2826	AGTCTGCAGTACTGGTTCT
siRNA 1085	1085	GAACCAGTACTGCAGACTA	2827	TAGTCTGCAGTACTGGTTC
siRNA 1086	1086	AACCAGTACTGCAGACTAT	2828	ATAGTCTGCAGTACTGGTT
siRNA 1087	1087	ACCAGTACTGCAGACTATG	2829	CATAGTCTGCAGTACTGGT
siRNA 1088	1088	CCAGTACTGCAGACTATGC	2830	GCATAGTCTGCAGTACTGG
siRNA 1089	1089	CAGTACTGCAGACTATGCC	2831	GGCATAGTCTGCAGTACTG
siRNA 1090	1090	AGTACTGCAGACTATGCCA	2832	TGGCATAGTCTGCAGTACT
siRNA 1091	1091	GTAAGTGCAGACTATGCCAT	2833	ATGGCATAGTCTGCAGTAC
siRNA 1092	1092	TACTGCAGACTATGCCATG	2834	CATGGCATAGTCTGCAGTA
siRNA 1093	1093	ACTGCAGACTATGCCATGT	2835	ACATGGCATAGTCTGCAGT
siRNA 1094	1094	CTGCAGACTATGCCATGTT	2836	AACATGGCATAGTCTGCAG
siRNA 1095	1095	TGCAGACTATGCCATGTTT	2837	GAACATGGCATAGTCTGCA
siRNA 1096	1096	GCAGACTATGCCATGTTCA	2838	TGAACATGGCATAGTCTGC
siRNA 1097	1097	CAGACTATGCCATGTTCAA	2839	TTGAACATGGCATAGTCTG
siRNA 1098	1098	AGACTATGCCATGTTCAAG	2840	CTTGAACATGGCATAGTCT
siRNA 1099	1099	GACTATGCCATGTTCAAGG	2841	CCTTGAACATGGCATAGTC
siRNA 1100	1100	ACTATGCCATGTTCAAGGT	2842	ACCTTGAACATGGCATAGT
siRNA 1101	1101	CTATGCCATGTTCAAGGTG	2843	CACCTTGAACATGGCATAG
siRNA 1102	1102	TATGCCATGTTCAAGGTGG	2844	CCACCTTGAACATGGCATA
siRNA 1103	1103	ATGCCATGTTCAAGGTGGG	2845	CCCACCTTGAACATGGCAT
siRNA 1104	1104	TGCCATGTTCAAGGTGGGA	2846	TCCCACCTTGAACATGGCA
siRNA 1105	1105	GCCATGTTCAAGGTGGGAC	2847	GTCCCACCTTGAACATGGC
siRNA 1106	1106	CCATGTTCAAGGTGGGACC	2848	GGTCCCACCTTGAACATGG
siRNA 1107	1107	CATGTTCAAGGTGGGACCT	2849	AGGTCCCACCTTGAACATG
siRNA 1108	1108	ATGTTCAAGGTGGGACCTG	2850	CAGGTCCCACCTTGAACAT
siRNA 1109	1109	TGTTCAAGGTGGGACCTGA	2851	TCAGGTCCCACCTTGAACA
siRNA 1110	1110	GTTCAAGGTGGGACCTGAA	2852	TTCAGGTCCCACCTTGAAC
siRNA 1111	1111	TTCAAGGTGGGACCTGAAG	2853	CTTCAGGTCCCACCTTGAA
siRNA 1112	1112	TCAAGGTGGGACCTGAAGC	2854	GCTTCAGGTCCCACCTTGA
siRNA 1113	1113	CAAGGTGGGACCTGAAGCT	2855	AGCTTCAGGTCCCACCTTG
siRNA 1114	1114	AAGGTGGGACCTGAAGCTG	2856	CAGCTTCAGGTCCCACCTT
siRNA 1115	1115	AGGTGGGACCTGAAGCTGA	2857	TCAGCTTCAGGTCCCACCT
siRNA 1116	1116	GGTGGGACCTGAAGCTGAC	2858	GTCAGCTTCAGGTCCCACC
siRNA 1117	1117	GTGGGACCTGAAGCTGACA	2859	TGTCAGCTTCAGGTCCCAC
siRNA 1118	1118	TGGGACCTGAAGCTGACAA	2860	TTGTCAGCTTCAGGTCCCC
siRNA 1119	1119	GGGACCTGAAGCTGACAAG	2861	CTTGTTCAGCTTCAGGTCCC
siRNA 1120	1120	GGACCTGAAGCTGACAAGT	2862	ACTTGTTCAGCTTCAGGTCC
siRNA 1121	1121	GACCTGAAGCTGACAAGTA	2863	TACTTGTTCAGCTTCAGGTC
siRNA 1122	1122	ACCTGAAGCTGACAAGTAC	2864	GTACTTGTTCAGCTTCAGGT
siRNA 1123	1123	CCTGAAGCTGACAAGTACC	2865	GGTACTTGTTCAGCTTCAGG
siRNA 1124	1124	CTGAAGCTGACAAGTACCG	2866	CGGTACTTGTTCAGCTTCAG
siRNA 1125	1125	TGAAGCTGACAAGTACCGC	2867	GCGGTACTTGTTCAGCTTCA
siRNA 1126	1126	GAAGCTGACAAGTACCGCC	2868	GGCGGTACTTGTTCAGCTTC
siRNA 1127	1127	AAGCTGACAAGTACCGCCT	2869	AGGCGGTACTTGTTCAGCTT
siRNA 1128	1128	AGCTGACAAGTACCGCCTA	2870	TAGGCGGTACTTGTTCAGCT
siRNA 1129	1129	GCTGACAAGTACCGCCTAA	2871	TTAGGCGGTACTTGTTCAGC
siRNA 1130	1130	CTGACAAGTACCGCCTAAC	2872	GTTAGGCGGTACTTGTTCAG

siRNA 1131	1131	TGACAAGTACCGCCTAACACA	2873	TGTTAGGCGGTACTTGTCA
siRNA 1132	1132	GACAAGTACCGCCTAACAT	2874	ATGTTAGGCGGTACTTGTCT
siRNA 1133	1133	ACAAGTACCGCCTAACATA	2875	TATGTTAGGCGGTACTTGT
siRNA 1134	1134	CAAGTACCGCCTAACATAT	2876	ATATGTTAGGCGGTACTTG
siRNA 1135	1135	AAGTACCGCCTAACATATG	2877	CATATGTTAGGCGGTACTT
siRNA 1136	1136	AGTACCGCCTAACATATGC	2878	GCATATGTTAGGCGGTACT
siRNA 1137	1137	GTACCGCCTAACATATGCC	2879	GGCATATGTTAGGCGGTACT
siRNA 1138	1138	TACCGCCTAACATATGCCT	2880	AGGCATATGTTAGGCGGTA
siRNA 1139	1139	ACCGCCTAACATATGCCTA	2881	TAGGCATATGTTAGGCGGT
siRNA 1140	1140	CCGCCTAACATATGCCTAC	2882	GTAGGCATATGTTAGGCGG
siRNA 1141	1141	CGCCTAACATATGCCTACT	2883	AGTAGGCATATGTTAGGCG
siRNA 1142	1142	GCCTAACATATGCCTACTT	2884	AAGTAGGCATATGTTAGGC
siRNA 1143	1143	CCTAACATATGCCTACTTC	2885	GAAGTAGGCATATGTTAGG
siRNA 1144	1144	CTAACATATGCCTACTTCG	2886	CGAAGTAGGCATATGTTAG
siRNA 1145	1145	TAACATATGCCTACTTCGC	2887	GCGAAGTAGGCATATGTTA
siRNA 1146	1146	AACATATGCCTACTTCGCT	2888	AGCGAAGTAGGCATATGTT
siRNA 1147	1147	ACATATGCCTACTTCGCTG	2889	CAGCGAAGTAGGCATATGT
siRNA 1148	1148	CATATGCCTACTTCGCTGG	2890	CCAGCGAAGTAGGCATATG
siRNA 1149	1149	ATATGCCTACTTCGCTGGT	2891	ACCAGCGAAGTAGGCATAT
siRNA 1150	1150	TATGCCTACTTCGCTGGTG	2892	CACCAGCGAAGTAGGCATA
siRNA 1151	1151	ATGCCTACTTCGCTGGTGG	2893	CCACCAGCGAAGTAGGCAT
siRNA 1152	1152	TGCCTACTTCGCTGGTGGG	2894	CCCACCAGCGAAGTAGGCA
siRNA 1153	1153	GCCTACTTCGCTGGTGGGG	2895	CCCCACCAGCGAAGTAGGC
siRNA 1154	1154	CCTACTTCGCTGGTGGGGA	2896	TCCCCACCAGCGAAGTAGG
siRNA 1155	1155	CTACTTCGCTGGTGGGGAT	2897	ATCCCCACCAGCGAAGTAG
siRNA 1156	1156	TACTTCGCTGGTGGGGATG	2898	CATCCCCACCAGCGAAGTA
siRNA 1157	1157	ACTTCGCTGGTGGGGATGC	2899	GCATCCCCACCAGCGAAGT
siRNA 1158	1158	CTTCGCTGGTGGGGATGCT	2900	AGCATCCCCACCAGCGAAG
siRNA 1159	1159	TTCGCTGGTGGGGATGCTG	2901	CAGCATCCCCACCAGCGAA
siRNA 1160	1160	TCGCTGGTGGGGATGCTGG	2902	CCAGCATCCCCACCAGCGA
siRNA 1161	1161	CGCTGGTGGGGATGCTGGA	2903	TCCAGCATCCCCACCAGCG
siRNA 1162	1162	GCTGGTGGGGATGCTGGAG	2904	CTCCAGCATCCCCACCAGC
siRNA 1163	1163	CTGGTGGGGATGCTGGAGA	2905	TCTCCAGCATCCCCACCAG
siRNA 1164	1164	TGGTGGGGATGCTGGAGAT	2906	ATCTCCAGCATCCCCACCA
siRNA 1165	1165	GGTGGGGATGCTGGAGATG	2907	CATCTCCAGCATCCCCACC
siRNA 1166	1166	GTGGGGATGCTGGAGATGC	2908	GCATCTCCAGCATCCCCAC
siRNA 1167	1167	TGGGGATGCTGGAGATGCC	2909	GGCATCTCCAGCATCCCCA
siRNA 1168	1168	GGGGATGCTGGAGATGCCT	2910	AGGCATCTCCAGCATCCCC
siRNA 1169	1169	GGGATGCTGGAGATGCCTT	2911	AAGGCATCTCCAGCATCCC
siRNA 1170	1170	GGATGCTGGAGATGCCTTT	2912	AAAGGCATCTCCAGCATCC
siRNA 1171	1171	GATGCTGGAGATGCCTTTG	2913	CAAAGGCATCTCCAGCATC
siRNA 1172	1172	ATGCTGGAGATGCCTTTGA	2914	TCAAAGGCATCTCCAGCAT
siRNA 1173	1173	TGCTGGAGATGCCTTTGAT	2915	ATCAAAGGCATCTCCAGCA
siRNA 1174	1174	GCTGGAGATGCCTTTGATG	2916	CATCAAAGGCATCTCCAGC
siRNA 1175	1175	CTGGAGATGCCTTTGATGG	2917	CCATCAAAGGCATCTCCAG
siRNA 1176	1176	TGGAGATGCCTTTGATGGC	2918	GCCATCAAAGGCATCTCCA
siRNA 1177	1177	GGAGATGCCTTTGATGGCT	2919	AGCCATCAAAGGCATCTCC
siRNA 1178	1178	GAGATGCCTTTGATGGCTT	2920	AAGCCATCAAAGGCATCTC
siRNA 1179	1179	AGATGCCTTTGATGGCTTT	2921	AAAGCCATCAAAGGCATCT
siRNA 1180	1180	GATGCCTTTGATGGCTTTG	2922	CAAAGCCATCAAAGGCATC
siRNA 1181	1181	ATGCCTTTGATGGCTTTGA	2923	TCAAAGCCATCAAAGGCAT
siRNA 1182	1182	TGCCTTTGATGGCTTTGAT	2924	ATCAAAGCCATCAAAGGCA

siRNA 1183	1183	GCCTTTGATGGCTTTGATT	2925	AATCAAAGCCATCAAAGGC
siRNA 1184	1184	CCTTTGATGGCTTTGATT	2926	AAATCAAAGCCATCAAAGG
siRNA 1185	1185	CTTTGATGGCTTTGATTTT	2927	AAAATCAAAGCCATCAAAG
siRNA 1186	1186	TTTGATGGCTTTGATTTTG	2928	CAAAATCAAAGCCATCAAA
siRNA 1187	1187	TTGATGGCTTTGATTTTGG	2929	CCAAAATCAAAGCCATCAA
siRNA 1188	1188	TGATGGCTTTGATTTTGGC	2930	GCCAAAATCAAAGCCATCA
siRNA 1189	1189	GATGGCTTTGATTTTGGCG	2931	CGCCAAAATCAAAGCCATC
siRNA 1190	1190	ATGGCTTTGATTTTGGCGA	2932	TCGCCAAAATCAAAGCCAT
siRNA 1191	1191	TGGCTTTGATTTTGGCGAT	2933	ATCGCCAAAATCAAAGCCA
siRNA 1192	1192	GGCTTTGATTTTGGCGATG	2934	CATCGCCAAAATCAAAGCC
siRNA 1193	1193	GCTTTGATTTTGGCGATGA	2935	TCATCGCCAAAATCAAAGC
siRNA 1194	1194	CTTTGATTTTGGCGATGAT	2936	ATCATCGCCAAAATCAAAG
siRNA 1195	1195	TTTGATTTTGGCGATGATC	2937	GATCATCGCCAAAATCAAA
siRNA 1196	1196	TTGATTTTGGCGATGATCC	2938	GGATCATCGCCAAAATCAA
siRNA 1197	1197	TGATTTTGGCGATGATCCT	2939	AGGATCATCGCCAAAATCA
siRNA 1198	1198	GATTTTGGCGATGATCCTA	2940	TAGGATCATCGCCAAAATC
siRNA 1199	1199	ATTTTGGCGATGATCCTAG	2941	CTAGGATCATCGCCAAAAT
siRNA 1200	1200	TTTGGCGATGATCCTAGT	2942	ACTAGGATCATCGCCAAA
siRNA 1201	1201	TTTGGCGATGATCCTAGTG	2943	CACTAGGATCATCGCCAAA
siRNA 1202	1202	TTGGCGATGATCCTAGTGA	2944	TCCTAGGATCATCGCCAA
siRNA 1203	1203	TGGCGATGATCCTAGTGAC	2945	GTCCTAGGATCATCGCCA
siRNA 1204	1204	GGCGATGATCCTAGTGACA	2946	TGTCCTAGGATCATCGCC
siRNA 1205	1205	GCGATGATCCTAGTGACAA	2947	TTGTCTAGGATCATCGC
siRNA 1206	1206	CGATGATCCTAGTGACAAG	2948	CTGTCTAGGATCATCG
siRNA 1207	1207	GATGATCCTAGTGACAAGT	2949	ACTGTCTAGGATCATC
siRNA 1208	1208	ATGATCCTAGTGACAAGTT	2950	AACTGTCTAGGATCAT
siRNA 1209	1209	TGATCCTAGTGACAAGTTT	2951	AAACTGTCTAGGATCA
siRNA 1210	1210	GATCCTAGTGACAAGTTTT	2952	AAAACCTGTCTAGGATC
siRNA 1211	1211	ATCCTAGTGACAAGTTTTT	2953	AAAACTGTCTAGGAT
siRNA 1212	1212	TCCTAGTGACAAGTTTTTC	2954	GAAAACTGTCTAGGA
siRNA 1213	1213	CCTAGTGACAAGTTTTTCA	2955	TGAAAACTGTCTAGG
siRNA 1214	1214	CTAGTGACAAGTTTTTCAC	2956	GTGAAAACTGTCTAG
siRNA 1215	1215	TAGTGACAAGTTTTTCACA	2957	TGTGAAAACTGTCTACTA
siRNA 1216	1216	AGTGACAAGTTTTTCACAT	2958	ATGTGAAAACTGTCTACT
siRNA 1217	1217	GTGACAAGTTTTTCACATC	2959	GATGTGAAAACTGTCTAC
siRNA 1218	1218	TGACAAGTTTTTCACATCC	2960	GGATGTGAAAACTGTCTA
siRNA 1219	1219	GACAAGTTTTTCACATCCC	2961	GGGATGTGAAAACTGTCT
siRNA 1220	1220	ACAAGTTTTTCACATCCCA	2962	TGGGATGTGAAAACTTGT
siRNA 1221	1221	CAAGTTTTTCACATCCCAT	2963	ATGGGATGTGAAAACTTG
siRNA 1222	1222	AAGTTTTTCACATCCCAT	2964	TATGGGATGTGAAAACTT
siRNA 1223	1223	AGTTTTTCACATCCCAT	2965	TTATGGGATGTGAAAACT
siRNA 1224	1224	GTTTTTCACATCCCAT	2966	ATTATGGGATGTGAAAA
siRNA 1225	1225	TTTTTCACATCCCAT	2967	CATTATGGGATGTGAAAA
siRNA 1226	1226	TTTTCACATCCCAT	2968	CCATTATGGGATGTGAAAA
siRNA 1227	1227	TTTCACATCCCAT	2969	GCCATTATGGGATGTGAAA
siRNA 1228	1228	TTCACATCCCAT	2970	TGCCATTATGGGATGTGAA
siRNA 1229	1229	TCACATCCCAT	2971	ATGCCATTATGGGATGTGA
siRNA 1230	1230	CACATCCCAT	2972	CATGCCATTATGGGATGTG
siRNA 1231	1231	ACATCCCAT	2973	GCATGCCATTATGGGATGT
siRNA 1232	1232	CATCCCAT	2974	TGCATGCCATTATGGGATG
siRNA 1233	1233	ATCCCAT	2975	CTGCATGCCATTATGGGAT
siRNA 1234	1234	TCCCAT	2976	ACTGCATGCCATTATGGGA

siRNA 1235	1235	CCCATAATGGCATGCAGTT	2977	AACTGCATGCCATTATGGG
siRNA 1236	1236	CCATAATGGCATGCAGTTC	2978	GAACTGCATGCCATTATGG
siRNA 1237	1237	CATAATGGCATGCAGTTCA	2979	TGAACTGCATGCCATTATG
siRNA 1238	1238	ATAATGGCATGCAGTTCAG	2980	CTGAACTGCATGCCATTAT
siRNA 1239	1239	TAATGGCATGCAGTTCAGT	2981	ACTGAACTGCATGCCATTA
siRNA 1240	1240	AATGGCATGCAGTTCAGTA	2982	TACTGAACTGCATGCCATT
siRNA 1241	1241	ATGGCATGCAGTTCAGTAC	2983	GTAAGTGCATGCCATTATG
siRNA 1242	1242	TGGCATGCAGTTCAGTACC	2984	GGTACTGAACTGCATGCCA
siRNA 1243	1243	GGCATGCAGTTCAGTACCT	2985	AGGTACTGAACTGCATGCC
siRNA 1244	1244	GCATGCAGTTCAGTACCTG	2986	CAGGTACTGAACTGCATGC
siRNA 1245	1245	CATGCAGTTCAGTACCTGG	2987	CCAGGTACTGAACTGCATG
siRNA 1246	1246	ATGCAGTTCAGTACCTGGG	2988	CCCAGGTACTGAACTGCAT
siRNA 1247	1247	TGCAGTTCAGTACCTGGGA	2989	TCCCAGGTACTGAACTGCA
siRNA 1248	1248	GCAGTTCAGTACCTGGGAC	2990	GTCCCAGGTACTGAACTGC
siRNA 1249	1249	CAGTTCAGTACCTGGGACA	2991	TGTCCCAGGTACTGAACTG
siRNA 1250	1250	AGTTCAGTACCTGGGACAA	2992	TTGTCCCAGGTACTGAACT
siRNA 1251	1251	GTTCAGTACCTGGGACAAT	2993	ATTGTCCCAGGTACTGAAC
siRNA 1252	1252	TTCAGTACCTGGGACAATG	2994	CATTGTCCCAGGTACTGAA
siRNA 1253	1253	TCAGTACCTGGGACAATGA	2995	TCATTGTCCCAGGTACTGA
siRNA 1254	1254	CAGTACCTGGGACAATGAC	2996	GTCATTGTCCCAGGTACTG
siRNA 1255	1255	AGTACCTGGGACAATGACA	2997	TGTCATTGTCCCAGGTACT
siRNA 1256	1256	GTACCTGGGACAATGACAA	2998	TTGTCATTGTCCCAGGTAC
siRNA 1257	1257	TACCTGGGACAATGACAAT	2999	ATTGTCATTGTCCCAGGTA
siRNA 1258	1258	ACCTGGGACAATGACAATG	3000	CATTGTTCATTGTCCCAGGT
siRNA 1259	1259	CCTGGGACAATGACAATGA	3001	TCATTGTTCATTGTCCCAGG
siRNA 1260	1260	CTGGGACAATGACAATGAT	3002	ATCATTGTTCATTGTCCCAG
siRNA 1261	1261	TGGGACAATGACAATGATA	3003	TATCATTGTTCATTGTCCCA
siRNA 1262	1262	GGGACAATGACAATGATAA	3004	TTATCATTGTTCATTGTCCC
siRNA 1263	1263	GGACAATGACAATGATAAG	3005	CTTATCATTGTTCATTGTCC
siRNA 1264	1264	GACAATGACAATGATAAGT	3006	ACTTATCATTGTTCATTGTC
siRNA 1265	1265	ACAATGACAATGATAAGTT	3007	AACTTATCATTGTTCATTGT
siRNA 1266	1266	CAATGACAATGATAAGTTT	3008	AACTTATCATTGTTCATTG
siRNA 1267	1267	AATGACAATGATAAGTTTG	3009	CAAACCTTATCATTGTTCAT
siRNA 1268	1268	ATGACAATGATAAGTTTGA	3010	TCAAACCTTATCATTGTCA
siRNA 1269	1269	TGACAATGATAAGTTTGAA	3011	TTCAAACCTTATCATTGTCA
siRNA 1270	1270	GACAATGATAAGTTTGAAG	3012	CTTCAAACCTTATCATTGTC
siRNA 1271	1271	ACAATGATAAGTTTGAAGG	3013	CCTTCAAACCTTATCATTGT
siRNA 1272	1272	CAATGATAAGTTTGAAGGC	3014	GCCTTCAAACCTTATCATTG
siRNA 1273	1273	AATGATAAGTTTGAAGGCA	3015	TGCCTTCAAACCTTATCATT
siRNA 1274	1274	ATGATAAGTTTGAAGGCAA	3016	TTGCCTTCAAACCTTATCAT
siRNA 1275	1275	TGATAAGTTTGAAGGCAAC	3017	GTTGCCTTCAAACCTTATCA
siRNA 1276	1276	GATAAGTTTGAAGGCAACT	3018	AGTTGCCTTCAAACCTTATC
siRNA 1277	1277	ATAAGTTTGAAGGCAACTG	3019	CAGTTGCCTTCAAACCTTAT
siRNA 1278	1278	TAAGTTTGAAGGCAACTGT	3020	ACAGTTGCCTTCAAACCTTA
siRNA 1279	1279	AAGTTTGAAGGCAACTGTG	3021	CACAGTTGCCTTCAAACCTT
siRNA 1280	1280	AGTTTGAAGGCAACTGTGC	3022	GCACAGTTGCCTTCAAACCT
siRNA 1281	1281	GTTTGAAGGCAACTGTGCT	3023	AGCACAGTTGCCTTCAAAC
siRNA 1282	1282	TTTGAAGGCAACTGTGCTG	3024	CAGCACAGTTGCCTTCAA
siRNA 1283	1283	TTGAAGGCAACTGTGCTGA	3025	TCAGCACAGTTGCCTTCAA
siRNA 1284	1284	TGAAGGCAACTGTGCTGAA	3026	TTCAGCACAGTTGCCTTCA
siRNA 1285	1285	GAAGGCAACTGTGCTGAAC	3027	GTTTCAGCACAGTTGCCTTC
siRNA 1286	1286	AAGGCAACTGTGCTGAACA	3028	TGTTTCAGCACAGTTGCCTT

siRNA 1287	1287	AGGCAACTGTGCTGAACAG	3029	CTGTTTCAGCACAGTTGCCT
siRNA 1288	1288	GGCAACTGTGCTGAACAGG	3030	CCTGTTTCAGCACAGTTGCC
siRNA 1289	1289	GCAACTGTGCTGAACAGGA	3031	TCCTGTTTCAGCACAGTTGC
siRNA 1290	1290	CAACTGTGCTGAACAGGAT	3032	ATCCTGTTTCAGCACAGTTG
siRNA 1291	1291	AACTGTGCTGAACAGGATG	3033	CATCCTGTTTCAGCACAGTT
siRNA 1292	1292	ACTGTGCTGAACAGGATGG	3034	CCATCCTGTTTCAGCACAGT
siRNA 1293	1293	CTGTGCTGAACAGGATGGA	3035	TCCATCCTGTTTCAGCACAG
siRNA 1294	1294	TGTGCTGAACAGGATGGAT	3036	ATCCATCCTGTTTCAGCACA
siRNA 1295	1295	GTGCTGAACAGGATGGATC	3037	GATCCATCCTGTTTCAGCAC
siRNA 1296	1296	TGCTGAACAGGATGGATCT	3038	AGATCCATCCTGTTTCAGCA
siRNA 1297	1297	GCTGAACAGGATGGATCTG	3039	CAGATCCATCCTGTTTCAGC
siRNA 1298	1298	CTGAACAGGATGGATCTGG	3040	CCAGATCCATCCTGTTTCAG
siRNA 1299	1299	TGAACAGGATGGATCTGGT	3041	ACCAGATCCATCCTGTTTCA
siRNA 1300	1300	GAACAGGATGGATCTGGTT	3042	AACCAGATCCATCCTGTTT
siRNA 1301	1301	AACAGGATGGATCTGGTTG	3043	CAACCAGATCCATCCTGTT
siRNA 1302	1302	ACAGGATGGATCTGGTTGG	3044	CCAACCAGATCCATCCTGT
siRNA 1303	1303	CAGGATGGATCTGGTTGGT	3045	ACCAACCAGATCCATCCTG
siRNA 1304	1304	AGGATGGATCTGGTTGGTG	3046	CACCAACCAGATCCATCCT
siRNA 1305	1305	GGATGGATCTGGTTGGTGG	3047	CCACCAACCAGATCCATCC
siRNA 1306	1306	GATGGATCTGGTTGGTGGG	3048	TCCACCAACCAGATCCATC
siRNA 1307	1307	ATGGATCTGGTTGGTGGAT	3049	ATCCACCAACCAGATCCAT
siRNA 1308	1308	TGGATCTGGTTGGTGGATG	3050	CATCCACCAACCAGATCCA
siRNA 1309	1309	GGATCTGGTTGGTGGATGA	3051	TCATCCACCAACCAGATCC
siRNA 1310	1310	GATCTGGTTGGTGGATGAA	3052	TTCATCCACCAACCAGATC
siRNA 1311	1311	ATCTGGTTGGTGGATGAAC	3053	GTTTCATCCACCAACCAGAT
siRNA 1312	1312	TCTGGTTGGTGGATGAACA	3054	TGTTTCATCCACCAACCAGA
siRNA 1313	1313	CTGGTTGGTGGATGAACAA	3055	TTGTTTCATCCACCAACCAG
siRNA 1314	1314	TGGTTGGTGGATGAACAAG	3056	CTTGTTTCATCCACCAACCA
siRNA 1315	1315	GGTTGGTGGATGAACAAGT	3057	ACTTGTTTCATCCACCAACC
siRNA 1316	1316	GTTGGTGGATGAACAAGTG	3058	CAC TTGTTTCATCCACCAAC
siRNA 1317	1317	TTGGTGGATGAACAAGTGT	3059	ACACTTGTTTCATCCACCAA
siRNA 1318	1318	TGGTGGATGAACAAGTGTC	3060	GACACTTGTTTCATCCACCA
siRNA 1319	1319	GGTGGATGAACAAGTGTC	3061	TGACACTTGTTTCATCCACC
siRNA 1320	1320	GTGGATGAACAAGTGTCAC	3062	GTGACACTTGTTTCATCCAC
siRNA 1321	1321	TGGATGAACAAGTGTCACG	3063	CGTGACACTTGTTTCATCCA
siRNA 1322	1322	GGATGAACAAGTGTCACGC	3064	GCGTGACACTTGTTTCATCC
siRNA 1323	1323	GATGAACAAGTGTCACGCT	3065	AGCGTGACACTTGTTTCATC
siRNA 1324	1324	ATGAACAAGTGTCACGCTG	3066	CAGCGTGACACTTGTTTCAT
siRNA 1325	1325	TGAACAAGTGTCACGCTGG	3067	CCAGCGTGACACTTGTTTCA
siRNA 1326	1326	GAACAAGTGTCACGCTGGC	3068	GCCAGCGTGACACTTGTTTC
siRNA 1327	1327	AACAAGTGTCACGCTGGCC	3069	GGCCAGCGTGACACTTGTT
siRNA 1328	1328	ACAAGTGTCACGCTGGCCA	3070	TGGCCAGCGTGACACTTGT
siRNA 1329	1329	CAAGTGTCACGCTGGCCAT	3071	ATGGCCAGCGTGACACTTG
siRNA 1330	1330	AAGTGTCACGCTGGCCATC	3072	GATGGCCAGCGTGACACTT
siRNA 1331	1331	AGTGTCACGCTGGCCATCT	3073	AGATGGCCAGCGTGACACT
siRNA 1332	1332	GTGTCACGCTGGCCATCTC	3074	GAGATGGCCAGCGTGACAC
siRNA 1333	1333	TGTCACGCTGGCCATCTCA	3075	TGAGATGGCCAGCGTGACA
siRNA 1334	1334	GTCACGCTGGCCATCTCAA	3076	TTGAGATGGCCAGCGTGAC
siRNA 1335	1335	TCACGCTGGCCATCTCAAT	3077	ATTGAGATGGCCAGCGTGA
siRNA 1336	1336	CACGCTGGCCATCTCAATG	3078	CATTGAGATGGCCAGCGTG
siRNA 1337	1337	ACGCTGGCCATCTCAATGG	3079	CCATTGAGATGGCCAGCGT
siRNA 1338	1338	CGCTGGCCATCTCAATGGA	3080	TCCATTGAGATGGCCAGCG

siRNA 1339	1339	GCTGGCCATCTCAATGGAG	3081	CTCCATTGAGATGGCCAGC
siRNA 1340	1340	CTGGCCATCTCAATGGAGT	3082	ACTCCATTGAGATGGCCAG
siRNA 1341	1341	TGGCCATCTCAATGGAGTT	3083	AACTCCATTGAGATGGCCA
siRNA 1342	1342	GGCCATCTCAATGGAGTTT	3084	AAACTCCATTGAGATGGCC
siRNA 1343	1343	GCCATCTCAATGGAGTTTA	3085	TAAACTCCATTGAGATGGC
siRNA 1344	1344	CCATCTCAATGGAGTTTAT	3086	ATAAACTCCATTGAGATGG
siRNA 1345	1345	CATCTCAATGGAGTTTATT	3087	AATAAACTCCATTGAGATG
siRNA 1346	1346	ATCTCAATGGAGTTTATTA	3088	TAATAAACTCCATTGAGAT
siRNA 1347	1347	TCTCAATGGAGTTTATTAC	3089	GTAATAAACTCCATTGAGA
siRNA 1348	1348	CTCAATGGAGTTTATTACC	3090	GGTAATAAACTCCATTGAG
siRNA 1349	1349	TCAATGGAGTTTATTACCA	3091	TGGTAATAAACTCCATTGA
siRNA 1350	1350	CAATGGAGTTTATTACCAA	3092	TTGGTAATAAACTCCATTG
siRNA 1351	1351	AATGGAGTTTATTACCAAG	3093	CTTGGTAATAAACTCCATT
siRNA 1352	1352	ATGGAGTTTATTACCAAGG	3094	CCTTGGTAATAAACTCCAT
siRNA 1353	1353	TGGAGTTTATTACCAAGGT	3095	ACCTTGGTAATAAACTCCA
siRNA 1354	1354	GGAGTTTATTACCAAGGTG	3096	CACCTTGGTAATAAACTCC
siRNA 1355	1355	GAGTTTATTACCAAGGTGG	3097	CCACCTTGGTAATAAACTC
siRNA 1356	1356	AGTTTATTACCAAGGTGGC	3098	GCCACCTTGGTAATAAACT
siRNA 1357	1357	GTTTATTACCAAGGTGGCA	3099	TGCCACCTTGGTAATAAAC
siRNA 1358	1358	TTTATTACCAAGGTGGCAC	3100	GTGCCACCTTGGTAATAAAA
siRNA 1359	1359	TTATTACCAAGGTGGCACT	3101	AGTGCCACCTTGGTAATAA
siRNA 1360	1360	TATTACCAAGGTGGCACTT	3102	AAGTGCCACCTTGGTAATA
siRNA 1361	1361	ATTACCAAGGTGGCACTTA	3103	TAAGTGCCACCTTGGTAAT
siRNA 1362	1362	TTACCAAGGTGGCACTTAC	3104	GTAAGTGCCACCTTGGTAA
siRNA 1363	1363	TACCAAGGTGGCACTTACT	3105	AGTAAGTGCCACCTTGGTA
siRNA 1364	1364	ACCAAGGTGGCACTTACTC	3106	GAGTAAGTGCCACCTTGGT
siRNA 1365	1365	CCAAGGTGGCACTTACTCA	3107	TGAGTAAGTGCCACCTTGG
siRNA 1366	1366	CAAGGTGGCACTTACTCAA	3108	TTGAGTAAGTGCCACCTTG
siRNA 1367	1367	AAGGTGGCACTTACTCAAA	3109	TTTGAGTAAGTGCCACCTT
siRNA 1368	1368	AGGTGGCACTTACTCAAAA	3110	TTTTGAGTAAGTGCCACCT
siRNA 1369	1369	GGTGGCACTTACTCAAAAAG	3111	CTTTTGAGTAAGTGCCACC
siRNA 1370	1370	GTGGCACTTACTCAAAAAGC	3112	GCTTTTGAGTAAGTGCCAC
siRNA 1371	1371	TGGCACTTACTCAAAAAGCA	3113	TGCTTTTGAGTAAGTGCCA
siRNA 1372	1372	GGCACTTACTCAAAAAGCAT	3114	ATGCTTTTGAGTAAGTGCC
siRNA 1373	1373	GCACTTACTCAAAAAGCATC	3115	GATGCTTTTGAGTAAGTGC
siRNA 1374	1374	CACTTACTCAAAAAGCATCT	3116	AGATGCTTTTGAGTAAGTG
siRNA 1375	1375	ACTTACTCAAAAAGCATCTA	3117	TAGATGCTTTTGAGTAAGT
siRNA 1376	1376	CTTACTCAAAAAGCATCTAC	3118	GTAGATGCTTTTGAGTAAG
siRNA 1377	1377	TTACTCAAAAAGCATCTACT	3119	AGTAGATGCTTTTGAGTAA
siRNA 1378	1378	TACTCAAAAAGCATCTACTC	3120	GAGTAGATGCTTTTGAGTA
siRNA 1379	1379	ACTCAAAAAGCATCTACTCC	3121	GGAGTAGATGCTTTTGAGT
siRNA 1380	1380	CTCAAAAAGCATCTACTCCT	3122	AGGAGTAGATGCTTTTGAG
siRNA 1381	1381	TCAAAAAGCATCTACTCCTA	3123	TAGGAGTAGATGCTTTTGGA
siRNA 1382	1382	CAAAAAGCATCTACTCCTAA	3124	TTAGGAGTAGATGCTTTTG
siRNA 1383	1383	AAAAGCATCTACTCCTAAT	3125	ATTAGGAGTAGATGCTTTT
siRNA 1384	1384	AAAGCATCTACTCCTAATG	3126	CATTAGGAGTAGATGCTTT
siRNA 1385	1385	AAGCATCTACTCCTAATGG	3127	CCATTAGGAGTAGATGCTT
siRNA 1386	1386	AGCATCTACTCCTAATGGT	3128	ACCATTAGGAGTAGATGCT
siRNA 1387	1387	GCATCTACTCCTAATGGTT	3129	AACCATTAGGAGTAGATGC
siRNA 1388	1388	CATCTACTCCTAATGGTTA	3130	TAACCATTAGGAGTAGATG
siRNA 1389	1389	ATCTACTCCTAATGGTTAT	3131	ATAACCATTAGGAGTAGAT
siRNA 1390	1390	TCTACTCCTAATGGTTATG	3132	CATAACCATTAGGAGTAGA

siRNA 1391	1391	CTACTCCTAATGGTTATGA	3133	TCATAACCATTAGGAGTAG
siRNA 1392	1392	TACTCCTAATGGTTATGAT	3134	ATCATAACCATTAGGAGTA
siRNA 1393	1393	ACTCCTAATGGTTATGATA	3135	TATCATAACCATTAGGAGT
siRNA 1394	1394	CTCCTAATGGTTATGATAA	3136	TTATCATAACCATTAGGAG
siRNA 1395	1395	TCCTAATGGTTATGATAAT	3137	ATTATCATAACCATTAGGA
siRNA 1396	1396	CCTAATGGTTATGATAATG	3138	CATTATCATAACCATTAGG
siRNA 1397	1397	CTAATGGTTATGATAATGG	3139	CCATTATCATAACCATTAG
siRNA 1398	1398	TAATGGTTATGATAATGGC	3140	GCCATTATCATAACCATTA
siRNA 1399	1399	AATGGTTATGATAATGGCA	3141	TGCCATTATCATAACCATT
siRNA 1400	1400	ATGGTTATGATAATGGCAT	3142	ATGCCATTATCATAACCAT
siRNA 1401	1401	TGGTTATGATAATGGCATT	3143	AATGCCATTATCATAACCA
siRNA 1402	1402	GGTTATGATAATGGCATT	3144	TAATGCCATTATCATAACC
siRNA 1403	1403	GTTATGATAATGGCATTAT	3145	ATAATGCCATTATCATAAC
siRNA 1404	1404	TTATGATAATGGCATTATT	3146	AATAATGCCATTATCATAA
siRNA 1405	1405	TATGATAATGGCATTATTT	3147	AAATAATGCCATTATCATA
siRNA 1406	1406	ATGATAATGGCATTATTTG	3148	CAAATAATGCCATTATCAT
siRNA 1407	1407	TGATAATGGCATTATTTGG	3149	CCAAATAATGCCATTATCA
siRNA 1408	1408	GATAATGGCATTATTTGGG	3150	CCCAAATAATGCCATTATC
siRNA 1409	1409	ATAATGGCATTATTTGGGC	3151	GCCCAAATAATGCCATTAT
siRNA 1410	1410	TAATGGCATTATTTGGGCC	3152	GGCCCAAATAATGCCATTA
siRNA 1411	1411	AATGGCATTATTTGGGCCA	3153	TGGCCCAAATAATGCCATT
siRNA 1412	1412	ATGGCATTATTTGGGCCAC	3154	GTGGCCCAAATAATGCCAT
siRNA 1413	1413	TGGCATTATTTGGGCCACT	3155	AGTGGCCCAAATAATGCCA
siRNA 1414	1414	GGCATTATTTGGGCCACTT	3156	AAGTGGCCCAAATAATGCC
siRNA 1415	1415	GCATTATTTGGGCCACTTG	3157	CAAGTGGCCCAAATAATGC
siRNA 1416	1416	CATTATTTGGGCCACTTGG	3158	CCAAGTGGCCCAAATAATG
siRNA 1417	1417	ATTATTTGGGCCACTTGGA	3159	TCCAAGTGGCCCAAATAAT
siRNA 1418	1418	TTATTTGGGCCACTTGGA	3160	TTCCAAGTGGCCCAAATAA
siRNA 1419	1419	TATTTGGGCCACTTGGA	3161	TTTCCAAGTGGCCCAAATA
siRNA 1420	1420	ATTTGGGCCACTTGGA	3162	TTTTCCAAGTGGCCCAAAT
siRNA 1421	1421	TTTGGGCCACTTGGA	3163	GTTTTCCAAGTGGCCCAA
siRNA 1422	1422	TTGGGCCACTTGGA	3164	GGTTTTCCAAGTGGCCCAA
siRNA 1423	1423	TGGGCCACTTGGA	3165	GGGTTTTCCAAGTGGCCCA
siRNA 1424	1424	GGGCCACTTGGA	3166	CGGGTTTTCCAAGTGGCCC
siRNA 1425	1425	GGCCACTTGGA	3167	CCGGGTTTTCCAAGTGGCC
siRNA 1426	1426	GCCACTTGGA	3168	ACCGGGTTTTCCAAGTGGC
siRNA 1427	1427	CCACTTGGA	3169	CACCGGGTTTTCCAAGTGG
siRNA 1428	1428	CACTTGGA	3170	CCACCGGGTTTTCCAAGTG
siRNA 1429	1429	ACTTGGA	3171	ACCACCGGGTTTTCCAAGT
siRNA 1430	1430	CTTGGA	3172	TACCACCGGGTTTTCCAAG
siRNA 1431	1431	TTGGA	3173	ATACCACCGGGTTTTCCA
siRNA 1432	1432	TGGA	3174	AATACCACCGGGTTTTCCA
siRNA 1433	1433	GGAA	3175	GAATACCACCGGGTTTTCC
siRNA 1434	1434	GAA	3176	GGAATACCACCGGGTTTTCC
siRNA 1435	1435	AAA	3177	TGGAATACCACCGGGTTTT
siRNA 1436	1436	AA	3178	ATGGAATACCACCGGGTTT
siRNA 1437	1437	A	3179	CATGGAATACCACCGGGTT
siRNA 1438	1438		3180	TCATGGAATACCACCGGGT
siRNA 1439	1439		3181	TTCATGGAATACCACCGGG
siRNA 1440	1440		3182	CTTCATGGAATACCACCGG
siRNA 1441	1441		3183	TCTTCATGGAATACCACCG
siRNA 1442	1442		3184	TTCTTCATGGAATACCACC

siRNA 1443	1443	GTGGTATTCCATGAAGAAA	3185	TTTCTTCATGGAATACCAC
siRNA 1444	1444	TGGTATTCCATGAAGAAAA	3186	TTTTCTTCATGGAATACCA
siRNA 1445	1445	GGTATTCCATGAAGAAAAC	3187	GTTTTCTTCATGGAATACC
siRNA 1446	1446	GTATTCCATGAAGAAAACC	3188	GGTTTTCTTCATGGAATAC
siRNA 1447	1447	TATTCCATGAAGAAAACCA	3189	TGGTTTTCTTCATGGAATA
siRNA 1448	1448	ATTCCATGAAGAAAACCAC	3190	GTGGTTTTCTTCATGGAAT
siRNA 1449	1449	TTCCATGAAGAAAACCACT	3191	AGTGGTTTTCTTCATGGAA
siRNA 1450	1450	TCCATGAAGAAAACCACTA	3192	TAGTGGTTTTCTTCATGGA
siRNA 1451	1451	CCATGAAGAAAACCACTAT	3193	ATAGTGGTTTTCTTCATGG
siRNA 1452	1452	CATGAAGAAAACCACTATG	3194	CATAGTGGTTTTCTTCATG
siRNA 1453	1453	ATGAAGAAAACCACTATGA	3195	TCATAGTGGTTTTCTTCAT
siRNA 1454	1454	TGAAGAAAACCACTATGAA	3196	TTCATAGTGGTTTTCTTCA
siRNA 1455	1455	GAAGAAAACCACTATGAAG	3197	CTTCATAGTGGTTTTCTTC
siRNA 1456	1456	AAGAAAACCACTATGAAGA	3198	TCTTCATAGTGGTTTTCTT
siRNA 1457	1457	AGAAAACCACTATGAAGAT	3199	ATCTTCATAGTGGTTTTCT
siRNA 1458	1458	GAAAACCACTATGAAGATA	3200	TATCTTCATAGTGGTTTTCT
siRNA 1459	1459	AAAACCACTATGAAGATAA	3201	TTATCTTCATAGTGGTTTT
siRNA 1460	1460	AAACCACTATGAAGATAAT	3202	ATTATCTTCATAGTGGTTT
siRNA 1461	1461	AACCACTATGAAGATAATC	3203	GATTATCTTCATAGTGGTT
siRNA 1462	1462	ACCACTATGAAGATAATCC	3204	GGATTATCTTCATAGTGGT
siRNA 1463	1463	CCACTATGAAGATAATCCC	3205	GGGATTATCTTCATAGTGG
siRNA 1464	1464	CACTATGAAGATAATCCCA	3206	TGGGATTATCTTCATAGTG
siRNA 1465	1465	ACTATGAAGATAATCCCAT	3207	ATGGGATTATCTTCATAGT
siRNA 1466	1466	CTATGAAGATAATCCCATT	3208	AATGGGATTATCTTCATAG
siRNA 1467	1467	TATGAAGATAATCCCATT	3209	GAATGGGATTATCTTCATA
siRNA 1468	1468	ATGAAGATAATCCCATTCA	3210	TGAATGGGATTATCTTCAT
siRNA 1469	1469	TGAAGATAATCCCATTCAA	3211	TTGAATGGGATTATCTTCA
siRNA 1470	1470	GAAGATAATCCCATTCAAC	3212	GTTGAATGGGATTATCTTC
siRNA 1471	1471	AAGATAATCCCATTCAACA	3213	TGTTGAATGGGATTATCTT
siRNA 1472	1472	AGATAATCCCATTCAACAG	3214	CTGTTGAATGGGATTATCT
siRNA 1473	1473	GATAATCCCATTCAACAGA	3215	TCTGTTGAATGGGATTATC
siRNA 1474	1474	ATAATCCCATTCAACAGAC	3216	GTCTGTTGAATGGGATTAT
siRNA 1475	1475	TAATCCCATTCAACAGACT	3217	AGTCTGTTGAATGGGATTAT
siRNA 1476	1476	AATCCCATTCAACAGACTC	3218	GAGTCTGTTGAATGGGATT
siRNA 1477	1477	ATCCCATTCAACAGACTCA	3219	TGAGTCTGTTGAATGGGAT
siRNA 1478	1478	TCCCATTCAACAGACTCAC	3220	GTGAGTCTGTTGAATGGGA
siRNA 1479	1479	CCCATTCAACAGACTCACA	3221	TGTGAGTCTGTTGAATGGG
siRNA 1480	1480	CCATTCAACAGACTCACAA	3222	TTGTGAGTCTGTTGAATGG
siRNA 1481	1481	CATTCAACAGACTCACAAAT	3223	ATTGTGAGTCTGTTGAATG
siRNA 1482	1482	ATTCAACAGACTCACAAAT	3224	AATTGTGAGTCTGTTGAAT
siRNA 1483	1483	TTCAACAGACTCACAAATG	3225	CAATTGTGAGTCTGTTGAA
siRNA 1484	1484	TCAACAGACTCACAAATGG	3226	CCAATTGTGAGTCTGTTGA
siRNA 1485	1485	CAACAGACTCACAAATGGA	3227	TCCAATTGTGAGTCTGTTG
siRNA 1486	1486	AACAGACTCACAAATGGAG	3228	CTCCAATTGTGAGTCTGTT
siRNA 1487	1487	ACAGACTCACAAATGGAGA	3229	TCTCCAATTGTGAGTCTGT
siRNA 1488	1488	CAGACTCACAAATGGAGAA	3230	TTCTCCAATTGTGAGTCTG
siRNA 1489	1489	AGACTCACAAATGGAGAAG	3231	CTTCTCCAATTGTGAGTCT
siRNA 1490	1490	GACTCACAAATGGAGAAGG	3232	CCTTCTCCAATTGTGAGTC
siRNA 1491	1491	ACTCACAAATGGAGAAGGA	3233	TCCTTCTCCAATTGTGAGT
siRNA 1492	1492	CTCACAAATGGAGAAGGAC	3234	GTCCTTCTCCAATTGTGAG
siRNA 1493	1493	TCACAAATGGAGAAGGACA	3235	TGTCCTTCTCCAATTGTGA
siRNA 1494	1494	CACAATGGAGAAGGACAG	3236	CTGTCCTTCTCCAATTGTG

siRNA 1495	1495	ACAATTGGAGAAGGACAGC	3237	GCTGTCCTTCTCCAATTGT
siRNA 1496	1496	CAATTGGAGAAGGACAGCA	3238	TGCTGTCCTTCTCCAATTG
siRNA 1497	1497	AATTGGAGAAGGACAGCAA	3239	TTGCTGTCCTTCTCCAATT
siRNA 1498	1498	ATTGGAGAAGGACAGCAAC	3240	GTTGCTGTCCTTCTCCAAT
siRNA 1499	1499	TTGGAGAAGGACAGCAACA	3241	TGTTGCTGTCCTTCTCCAA
siRNA 1500	1500	TGGAGAAGGACAGCAACAC	3242	GTGTTGCTGTCCTTCTCCA
siRNA 1501	1501	GGAGAAGGACAGCAACACC	3243	GGTGTGCTGTCCTTCTCC
siRNA 1502	1502	GAGAAGGACAGCAACACCA	3244	TGGTGTGCTGTCCTTCTC
siRNA 1503	1503	AGAAGGACAGCAACACCAC	3245	GTGGTGTGCTGTCCTTCT
siRNA 1504	1504	GAAGGACAGCAACACCACC	3246	GGTGGTGTGCTGTCCTTC
siRNA 1505	1505	AAGGACAGCAACACCACCT	3247	AGGTGGTGTGCTGTCCTT
siRNA 1506	1506	AGGACAGCAACACCACCTG	3248	CAGGTGGTGTGCTGTCTT
siRNA 1507	1507	GGACAGCAACACCACCTGG	3249	CCAGGTGGTGTGCTGTCC
siRNA 1508	1508	GACAGCAACACCACCTGGG	3250	CCCAGGTGGTGTGCTGTC
siRNA 1509	1509	ACAGCAACACCACCTGGGG	3251	CCCCAGGTGGTGTGCTGT
siRNA 1510	1510	CAGCAACACCACCTGGGGG	3252	CCCCCAGGTGGTGTGCTG
siRNA 1511	1511	AGCAACACCACCTGGGGGG	3253	CCCCCAGGTGGTGTGCTT
siRNA 1512	1512	GCAACACCACCTGGGGGGA	3254	TCCCCCAGGTGGTGTGTC
siRNA 1513	1513	CAACACCACCTGGGGGGAG	3255	CTCCCCCAGGTGGTGTTG
siRNA 1514	1514	AACACCACCTGGGGGGAGC	3256	GCTCCCCCAGGTGGTGTG
siRNA 1515	1515	ACACCACCTGGGGGGAGCC	3257	GGCTCCCCCAGGTGGTGT
siRNA 1516	1516	CACCACCTGGGGGGAGCCA	3258	TGGCTCCCCCAGGTGGTG
siRNA 1517	1517	ACCACCTGGGGGGAGCCAA	3259	TTGGCTCCCCCAGGTGGT
siRNA 1518	1518	CCACCTGGGGGGAGCCAAA	3260	TTTGGCTCCCCCAGGTGG
siRNA 1519	1519	CACCTGGGGGGAGCCAAAC	3261	GTTTGGCTCCCCCAGGTG
siRNA 1520	1520	ACCTGGGGGGAGCCAAACA	3262	TGTTTGGCTCCCCCAGGT
siRNA 1521	1521	CCTGGGGGGAGCCAAACAG	3263	CTGTTTGGCTCCCCCAGG
siRNA 1522	1522	CTGGGGGGAGCCAAACAGG	3264	CCTGTTTGGCTCCCCCAG
siRNA 1523	1523	TGGGGGGAGCCAAACAGGC	3265	GCCTGTTTGGCTCCCCCA
siRNA 1524	1524	GGGGGGAGCCAAACAGGCT	3266	AGCCTGTTTGGCTCCCCC
siRNA 1525	1525	GGGGGAGCCAAACAGGCTG	3267	CAGCCTGTTTGGCTCCCCC
siRNA 1526	1526	GGGGAGCCAAACAGGCTGG	3268	CCAGCCTGTTTGGCTCCCC
siRNA 1527	1527	GGGAGCCAAACAGGCTGGA	3269	TCCAGCCTGTTTGGCTCCC
siRNA 1528	1528	GGAGCCAAACAGGCTGGAG	3270	CTCCAGCCTGTTTGGCTCC
siRNA 1529	1529	GAGCCAAACAGGCTGGAGA	3271	TCTCCAGCCTGTTTGGCTC
siRNA 1530	1530	AGCCAAACAGGCTGGAGAC	3272	GTCTCCAGCCTGTTTGGCT
siRNA 1531	1531	GCCAAACAGGCTGGAGACG	3273	CGTCTCCAGCCTGTTTGGC
siRNA 1532	1532	CCAAACAGGCTGGAGACGT	3274	ACGTCTCCAGCCTGTTTGG
siRNA 1533	1533	CAAACAGGCTGGAGACGTT	3275	AACGTCTCCAGCCTGTTTG
siRNA 1534	1534	AAACAGGCTGGAGACGTTT	3276	AAACGTCTCCAGCCTGTTT
siRNA 1535	1535	AACAGGCTGGAGACGTTTA	3277	TAAACGTCTCCAGCCTGTT
siRNA 1536	1536	ACAGGCTGGAGACGTTTAA	3278	TTAAACGTCTCCAGCCTGT
siRNA 1537	1537	CAGGCTGGAGACGTTTAAA	3279	TTTAAACGTCTCCAGCCTG
siRNA 1538	1538	AGGCTGGAGACGTTTAAAA	3280	TTTTAAACGTCTCCAGCCT
siRNA 1539	1539	GGCTGGAGACGTTTAAAAG	3281	CTTTTAAACGTCTCCAGCC
siRNA 1540	1540	GCTGGAGACGTTTAAAAGA	3282	TCTTTTAAACGTCTCCAGC
siRNA 1541	1541	CTGGAGACGTTTAAAAGAC	3283	GTCTTTTAAACGTCTCCAG
siRNA 1542	1542	TGGAGACGTTTAAAAGACC	3284	GGTCTTTTAAACGTCTCCA
siRNA 1543	1543	GGAGACGTTTAAAAGACCG	3285	CGGTCTTTTAAACGTCTCC
siRNA 1544	1544	GAGACGTTTAAAAGACCGT	3286	ACGGTCTTTTAAACGTCTC
siRNA 1545	1545	AGACGTTTAAAAGACCGTT	3287	AACGGTCTTTTAAACGTCT
siRNA 1546	1546	GACGTTTAAAAGACCGTTT	3288	AAACGGTCTTTTAAACGTC

siRNA 1547	1547	ACGTTTAAAAGACCGTTTC	3289	GAAACGGTCTTTTAAACGT
siRNA 1548	1548	CGTTTAAAAGACCGTTTCA	3290	TGAAACGGTCTTTTAAACG
siRNA 1549	1549	GTTTAAAAGACCGTTTCAA	3291	TTGAAACGGTCTTTTAAAC
siRNA 1550	1550	TTTAAAAGACCGTTTCAAA	3292	TTTGAAACGGTCTTTTAAA
siRNA 1551	1551	TAAAAGACCGTTTCAAAA	3293	TTTGAAACGGTCTTTTAA
siRNA 1552	1552	TAAAAGACCGTTTCAAAAAG	3294	CTTTTGAAACGGTCTTTTA
siRNA 1553	1553	AAAAGACCGTTTCAAAAAGA	3295	TCTTTTGAAACGGTCTTTT
siRNA 1554	1554	AAAGACCGTTTCAAAAAGAG	3296	CTCTTTTGAAACGGTCTTT
siRNA 1555	1555	AAGACCGTTTCAAAAAGAGA	3297	TCTCTTTTGAAACGGTCTT
siRNA 1556	1556	AGACCGTTTCAAAAAGAGAT	3298	ATCTCTTTTGAAACGGTCT
siRNA 1557	1557	GACCGTTTCAAAAAGAGATT	3299	AATCTCTTTTGAAACGGTC
siRNA 1558	1558	ACCGTTTCAAAAAGAGATTT	3300	AAATCTCTTTTGAAACGGT
siRNA 1559	1559	CCGTTTCAAAAAGAGATTTA	3301	TAAATCTCTTTTGAAACGG
siRNA 1560	1560	CGTTTCAAAAAGAGATTTAC	3302	GTAAATCTCTTTTGAAACG
siRNA 1561	1561	GTTTCAAAAAGAGATTTACT	3303	AGTAAATCTCTTTTGAAAC
siRNA 1562	1562	TTTCAAAAAGAGATTTACTT	3304	AAGTAAATCTCTTTTGAAA
siRNA 1563	1563	TTCAAAAAGAGATTTACTTT	3305	AAAGTAAATCTCTTTTGAA
siRNA 1564	1564	TCAAAAAGAGATTTACTTTT	3306	AAAAGTAAATCTCTTTTGA
siRNA 1565	1565	CAAAAAGAGATTTACTTTTT	3307	AAAAAGTAAATCTCTTTTG
siRNA 1566	1566	AAAAGAGATTTACTTTTTT	3308	AAAAAGTAAATCTCTTTT
siRNA 1567	1567	AAAGAGATTTACTTTTTTA	3309	TAAAAAGTAAATCTCTTT
siRNA 1568	1568	AAGAGATTTACTTTTTTAA	3310	TTAAAAAGTAAATCTCTT
siRNA 1569	1569	AGAGATTTACTTTTTTAAA	3311	TTTAAAAAGTAAATCTCT
siRNA 1570	1570	GAGATTTACTTTTTTAAAG	3312	CTTTAAAAAGTAAATCTC
siRNA 1571	1571	AGATTTACTTTTTTAAAGG	3313	CCTTTAAAAAGTAAATCT
siRNA 1572	1572	GATTTACTTTTTTAAAGGA	3314	TCCTTTAAAAAGTAAATC
siRNA 1573	1573	ATTTACTTTTTTAAAGGAC	3315	GTCTTTAAAAAGTAAAT
siRNA 1574	1574	TTTACTTTTTTAAAGGACT	3316	AGTCCTTTAAAAAGTAAA
siRNA 1575	1575	TTACTTTTTTAAAGGACTT	3317	AAGTCCTTTAAAAAGTAA
siRNA 1576	1576	TACTTTTTTAAAGGACTTT	3318	AAAGTCCTTTAAAAAGTA
siRNA 1577	1577	ACTTTTTTAAAGGACTTTA	3319	TAAAGTCCTTTAAAAAGT
siRNA 1578	1578	CTTTTTTAAAGGACTTTAT	3320	ATAAAGTCCTTTAAAAAG
siRNA 1579	1579	TTTTTTAAAGGACTTTATC	3321	GATAAAGTCCTTTAAAAA
siRNA 1580	1580	TTTTTAAAGGACTTTATCT	3322	AGATAAAGTCCTTTAAAA
siRNA 1581	1581	TTTTAAAGGACTTTATCTG	3323	CAGATAAAGTCCTTTAAA
siRNA 1582	1582	TTTAAAGGACTTTATCTGA	3324	TCAGATAAAGTCCTTTAA
siRNA 1583	1583	TTAAAGGACTTTATCTGAA	3325	TTCAAGATAAAGTCCTTTA
siRNA 1584	1584	TAAAGGACTTTATCTGAAC	3326	GTTCAAGATAAAGTCCTTT
siRNA 1585	1585	AAAGGACTTTATCTGAACA	3327	TGTTCAAGATAAAGTCCTT
siRNA 1586	1586	AAGGACTTTATCTGAACAG	3328	CTGTTCAAGATAAAGTCCT
siRNA 1587	1587	AGGACTTTATCTGAACAGA	3329	TCTGTTCAAGATAAAGTCCT
siRNA 1588	1588	GGACTTTATCTGAACAGAG	3330	CTCTGTTCAAGATAAAGTCC
siRNA 1589	1589	GACTTTATCTGAACAGAGA	3331	TCTCTGTTCAAGATAAAGTC
siRNA 1590	1590	ACTTTATCTGAACAGAGAG	3332	CTCTCTGTTCAAGATAAAGT
siRNA 1591	1591	CTTTATCTGAACAGAGAGA	3333	TCTCTCTGTTCAAGATAAAG
siRNA 1592	1592	TTTATCTGAACAGAGAGAT	3334	ATCTCTCTGTTCAAGATAAA
siRNA 1593	1593	TTATCTGAACAGAGAGATA	3335	TATCTCTCTGTTCAAGATAA
siRNA 1594	1594	TATCTGAACAGAGAGATAT	3336	ATATCTCTCTGTTCAAGATA
siRNA 1595	1595	ATCTGAACAGAGAGATATA	3337	TATATCTCTCTGTTCAAGAT
siRNA 1596	1596	TCTGAACAGAGAGATATAA	3338	TTATATCTCTCTGTTCAGA
siRNA 1597	1597	CTGAACAGAGAGATATAAT	3339	ATTATATCTCTCTGTTCAG
siRNA 1598	1598	TGAACAGAGAGATATAATA	3340	TATTATATCTCTCTGTTCA

siRNA 1599	1599	GAACAGAGAGATATAATAT	3341	ATATTATATCTCTCTGTTT
siRNA 1600	1600	AACAGAGAGATATAATATT	3342	AATATTATATCTCTCTGTT
siRNA 1601	1601	ACAGAGAGATATAATATTT	3343	AAATATTATATCTCTCTGT
siRNA 1602	1602	CAGAGAGATATAATATTTT	3344	AAAATATTATATCTCTCTG
siRNA 1603	1603	AGAGAGATATAATATTTTT	3345	AAAAATATTATATCTCTCT
siRNA 1604	1604	GAGAGATATAATATTTTTTC	3346	GAAAAATATTATATCTCTC
siRNA 1605	1605	AGAGATATAATATTTTTTCC	3347	GGAAAAATATTATATCTCT
siRNA 1606	1606	GAGATATAATATTTTTTCCT	3348	AGGAAAAATATTATATCTC
siRNA 1607	1607	AGATATAATATTTTTTCCTA	3349	TAGGAAAAATATTATATCT
siRNA 1608	1608	GATATAATATTTTTTCCTAT	3350	ATAGGAAAAATATTATATC
siRNA 1609	1609	ATATAATATTTTTTCCTATT	3351	AATAGGAAAAATATTATAT
siRNA 1610	1610	TATAATATTTTTTCCTATTG	3352	CAATAGGAAAAATATTATA
siRNA 1611	1611	ATAATATTTTTTCCTATTGG	3353	CCAATAGGAAAAATATTAT
siRNA 1612	1612	TAATATTTTTTCCTATTGGA	3354	TCCAATAGGAAAAATATTA
siRNA 1613	1613	AATATTTTTTCCTATTGGAC	3355	GTCCAATAGGAAAAATATT
siRNA 1614	1614	ATATTTTTTCCTATTGGACA	3356	TGTCCAATAGGAAAAATAT
siRNA 1615	1615	TATTTTTTCCTATTGGACAA	3357	TTGTCCAATAGGAAAAATA
siRNA 1616	1616	ATTTTTTCCTATTGGACAAT	3358	ATTGTCCAATAGGAAAAAT
siRNA 1617	1617	TTTTTCCTATTGGACAATG	3359	CATTGTCCAATAGGAAAAA
siRNA 1618	1618	TTTTCCTATTGGACAATGG	3360	CCATTGTCCAATAGGAAAA
siRNA 1619	1619	TTTCCTATTGGACAATGGA	3361	TCCATTGTCCAATAGGAAA
siRNA 1620	1620	TTCCTATTGGACAATGGAC	3362	GTCCATTGTCCAATAGGAA
siRNA 1621	1621	TCCTATTGGACAATGGACT	3363	AGTCCATTGTCCAATAGGA
siRNA 1622	1622	CCTATTGGACAATGGACTT	3364	AAGTCCATTGTCCAATAGG
siRNA 1623	1623	CTATTGGACAATGGACTTG	3365	CAAGTCCATTGTCCAATAG
siRNA 1624	1624	TATTGGACAATGGACTTGC	3366	GCAAGTCCATTGTCCAATA
siRNA 1625	1625	ATTGGACAATGGACTTGCA	3367	TGCAAGTCCATTGTCCAAT
siRNA 1626	1626	TTGGACAATGGACTTGCAA	3368	TTGCAAGTCCATTGTCCAA
siRNA 1627	1627	TGGACAATGGACTTGCAAA	3369	TTTGCAAGTCCATTGTCCA
siRNA 1628	1628	GGACAATGGACTTGCAAAG	3370	CTTTGCAAGTCCATTGTCC
siRNA 1629	1629	GACAATGGACTTGCAAAGC	3371	GCTTTGCAAGTCCATTGTG
siRNA 1630	1630	ACAATGGACTTGCAAAGCT	3372	AGCTTTGCAAGTCCATTGT
siRNA 1631	1631	CAATGGACTTGCAAAGCTT	3373	AAGCTTTGCAAGTCCATTG
siRNA 1632	1632	AATGGACTTGCAAAGCTTC	3374	GAAGCTTTGCAAGTCCATT
siRNA 1633	1633	ATGGACTTGCAAAGCTTCA	3375	TGAAGCTTTGCAAGTCCAT
siRNA 1634	1634	TGGACTTGCAAAGCTTCAC	3376	GTGAAGCTTTGCAAGTCCA
siRNA 1635	1635	GGACTTGCAAAGCTTCACT	3377	AGTGAAGCTTTGCAAGTCC
siRNA 1636	1636	GACTTGCAAAGCTTCACTT	3378	AAGTGAAGCTTTGCAAGTC
siRNA 1637	1637	ACTTGCAAAGCTTCACTTC	3379	GAAGTGAAGCTTTGCAAGT
siRNA 1638	1638	CTTGCAAAGCTTCACTTCA	3380	TGAAGTGAAGCTTTGCAAG
siRNA 1639	1639	TTGCAAAGCTTCACTTCAT	3381	ATGAAGTGAAGCTTTGCAA
siRNA 1640	1640	TGCAAAGCTTCACTTCATT	3382	AATGAAGTGAAGCTTTGCA
siRNA 1641	1641	GCAAAGCTTCACTTCATTT	3383	AAATGAAGTGAAGCTTTGC
siRNA 1642	1642	CAAAGCTTCACTTCATTTT	3384	AAAATGAAGTGAAGCTTTG
siRNA 1643	1643	AAAGCTTCACTTCATTTTA	3385	TAAAATGAAGTGAAGCTTT
siRNA 1644	1644	AAGCTTCACTTCATTTTAA	3386	TTAAAATGAAGTGAAGCTT
siRNA 1645	1645	AGCTTCACTTCATTTTAAG	3387	CTTAAAATGAAGTGAAGCT
siRNA 1646	1646	GCTTCACTTCATTTTAAGA	3388	TCTTAAAATGAAGTGAAGC
siRNA 1647	1647	CTTCACTTCATTTTAAGAG	3389	CTCTTAAAATGAAGTGAAG
siRNA 1648	1648	TTCCTTCATTTTAAGAGC	3390	GCTCTTAAAATGAAGTGAA
siRNA 1649	1649	TCACTTCATTTTAAGAGCA	3391	TGCTCTTAAAATGAAGTGA
siRNA 1650	1650	CACCTTCATTTTAAGAGCAA	3392	TTGCTCTTAAAATGAAGTG

siRNA 1651	1651	ACTTCATTTTAAGAGCAAA	3393	TTTGCTCTTAAAATGAAGT
siRNA 1652	1652	CTTCATTTTAAGAGCAAAA	3394	TTTTGCTCTTAAAATGAAG
siRNA 1653	1653	TTCATTTTAAGAGCAAAAG	3395	CTTTTGCTCTTAAAATGAA
siRNA 1654	1654	TCATTTTAAGAGCAAAAGA	3396	TCTTTTGCTCTTAAAATGA
siRNA 1655	1655	CATTTTAAGAGCAAAAGAC	3397	GTCTTTTGCTCTTAAAATG
siRNA 1656	1656	ATTTTAAGAGCAAAAGACC	3398	GGTCTTTTGCTCTTAAAAT
siRNA 1657	1657	TTTTAAGAGCAAAAGACCC	3399	GGGTCTTTTGCTCTTAAAA
siRNA 1658	1658	TTTAAGAGCAAAAGACCCC	3400	GGGGTCTTTTGCTCTTAAA
siRNA 1659	1659	TTAAGAGCAAAAGACCCCA	3401	TGGGGTCTTTTGCTCTTAA
siRNA 1660	1660	TAAGAGCAAAAGACCCCAT	3402	ATGGGGTCTTTTGCTCTTA
siRNA 1661	1661	AAGAGCAAAAGACCCCATG	3403	CATGGGGTCTTTTGCTCTT
siRNA 1662	1662	AGAGCAAAAGACCCCATGT	3404	ACATGGGGTCTTTTGCTCT
siRNA 1663	1663	GAGCAAAAGACCCCATGTT	3405	AACATGGGGTCTTTTGCTC
siRNA 1664	1664	AGCAAAAGACCCCATGTTG	3406	CAACATGGGGTCTTTTGCT
siRNA 1665	1665	GCAAAAGACCCCATGTTGA	3407	TCAACATGGGGTCTTTTGC
siRNA 1666	1666	CAAAAGACCCCATGTTGAA	3408	TTCAACATGGGGTCTTTTG
siRNA 1667	1667	AAAAGACCCCATGTTGAAA	3409	TTTCAACATGGGGTCTTTT
siRNA 1668	1668	AAAGACCCCATGTTGAAAA	3410	TTTTCAACATGGGGTCTTT
siRNA 1669	1669	AAGACCCCATGTTGAAAAC	3411	GTTTTCAACATGGGGTCTT
siRNA 1670	1670	AGACCCCATGTTGAAAAC	3412	AGTTTTCAACATGGGGTCT
siRNA 1671	1671	GACCCCATGTTGAAAAC	3413	GAGTTTTCAACATGGGGTC
siRNA 1672	1672	ACCCCATGTTGAAAAC	3414	GGAGTTTTCAACATGGGGT
siRNA 1673	1673	CCCCATGTTGAAAAC	3415	TGGAGTTTTCAACATGGGG
siRNA 1674	1674	CCCATGTTGAAAAC	3416	ATGGAGTTTTCAACATGGG
siRNA 1675	1675	CCATGTTGAAAAC	3417	TATGGAGTTTTCAACATGG
siRNA 1676	1676	CATGTTGAAAAC	3418	TTATGGAGTTTTCAACATG
siRNA 1677	1677	ATGTTGAAAAC	3419	GTTATGGAGTTTTCAACAT
siRNA 1678	1678	TGTTGAAAAC	3420	TGTTATGGAGTTTTCAACA
siRNA 1679	1679	GTTGAAAAC	3421	CTGTTATGGAGTTTTCAAC
siRNA 1680	1680	TTGAAAAC	3422	ACTGTTATGGAGTTTTCAA
siRNA 1681	1681	TGAAAAC	3423	AACTGTTATGGAGTTTTCA
siRNA 1682	1682	GAAAAC	3424	AACTGTTATGGAGTTTTTC
siRNA 1683	1683	AAAAC	3425	AACTGTTATGGAGTTTTT
siRNA 1684	1684	AAAC	3426	TAAAAC
siRNA 1685	1685	AACTCCATAACAGTTTTT	3427	ATAAACTGTTATGGAGTT
siRNA 1686	1686	ACTCCATAACAGTTTTATG	3428	CATAAACTGTTATGGAGT
siRNA 1687	1687	CTCCATAACAGTTTTATGC	3429	GCATAAACTGTTATGGAG
siRNA 1688	1688	TCCATAACAGTTTTATGCT	3430	AGCATAAACTGTTATGGA
siRNA 1689	1689	CCATAACAGTTTTATGCTG	3431	CAGCATAAACTGTTATGG
siRNA 1690	1690	CATAACAGTTTTATGCTGA	3432	TCAGCATAAACTGTTATG
siRNA 1691	1691	ATAACAGTTTTATGCTGAT	3433	ATCAGCATAAACTGTTAT
siRNA 1692	1692	TAACAGTTTTATGCTGATG	3434	CATCAGCATAAACTGTTA
siRNA 1693	1693	AACAGTTTTATGCTGATGA	3435	TCATCAGCATAAACTGTT
siRNA 1694	1694	ACAGTTTTATGCTGATGAT	3436	ATCATCAGCATAAACTGT
siRNA 1695	1695	CAGTTTTATGCTGATGATA	3437	TATCATCAGCATAAACTG
siRNA 1696	1696	AGTTTTATGCTGATGATAA	3438	TTATCATCAGCATAAACT
siRNA 1697	1697	GTTTTATGCTGATGATAAT	3439	ATTATCATCAGCATAAAAC
siRNA 1698	1698	TTTTATGCTGATGATAATT	3440	AATTATCATCAGCATAAAA
siRNA 1699	1699	TTTATGCTGATGATAATTT	3441	AAATTATCATCAGCATAAA
siRNA 1700	1700	TTATGCTGATGATAATTTA	3442	TAAATTATCATCAGCATAA
siRNA 1701	1701	TATGCTGATGATAATTTAT	3443	ATAAATTATCATCAGCATA
siRNA 1702	1702	ATGCTGATGATAATTTATC	3444	GATAAATTATCATCAGCAT

siRNA 1703	1703	TGCTGATGATAATTTATCT	3445	AGATAAAATTATCATCAGCA
siRNA 1704	1704	GCTGATGATAATTTATCTA	3446	TAGATAAAATTATCATCAGC
siRNA 1705	1705	CTGATGATAATTTATCTAC	3447	GTAGATAAAATTATCATCAG
siRNA 1706	1706	TGATGATAATTTATCTACA	3448	TGTAGATAAAATTATCATCA
siRNA 1707	1707	GATGATAATTTATCTACAT	3449	ATGTAGATAAAATTATCATC
siRNA 1708	1708	ATGATAATTTATCTACATG	3450	CATGTAGATAAAATTATCAT
siRNA 1709	1709	TGATAATTTATCTACATGC	3451	GCATGTAGATAAAATTATCA
siRNA 1710	1710	GATAATTTATCTACATGCA	3452	TGCATGTAGATAAAATTATC
siRNA 1711	1711	ATAATTTATCTACATGCAT	3453	ATGCATGTAGATAAAATTAT
siRNA 1712	1712	TAATTTATCTACATGCATT	3454	AATGCATGTAGATAAAATTA
siRNA 1713	1713	AATTTATCTACATGCATTT	3455	AAATGCATGTAGATAAAATT
siRNA 1714	1714	ATTTATCTACATGCATTTT	3456	GAAATGCATGTAGATAAAAT
siRNA 1715	1715	TTTATCTACATGCATTTCA	3457	TGAAATGCATGTAGATAAAA
siRNA 1716	1716	TTATCTACATGCATTTCAA	3458	TTGAAATGCATGTAGATAAA
siRNA 1717	1717	TATCTACATGCATTTCAAT	3459	ATTGAAATGCATGTAGATA
siRNA 1718	1718	ATCTACATGCATTTCAATA	3460	TATTGAAATGCATGTAGAT
siRNA 1719	1719	TCTACATGCATTTCAATAA	3461	TTATTGAAATGCATGTAGA
siRNA 1720	1720	CTACATGCATTTCAATAAA	3462	TTATTGAAATGCATGTAG
siRNA 1721	1721	TACATGCATTTCAATAAAC	3463	GTTTATTGAAATGCATGTA
siRNA 1722	1722	ACATGCATTTCAATAAAC	3464	GGTTTATTGAAATGCATGT
siRNA 1723	1723	CATGCATTTCAATAAACCT	3465	AGGTTTATTGAAATGCATG
siRNA 1724	1724	ATGCATTTCAATAAACCTT	3466	AAGGTTTATTGAAATGCAT
siRNA 1725	1725	TGCATTTCAATAAACCTTT	3467	AAAGGTTTATTGAAATGCA
siRNA 1726	1726	GCATTTCAATAAACCTTTT	3468	AAAAGGTTTATTGAAATGC
siRNA 1727	1727	CATTTCAATAAACCTTTTG	3469	CAAAAGGTTTATTGAAATG
siRNA 1728	1728	ATTTCAATAAACCTTTTGT	3470	ACAAAAGGTTTATTGAAAT
siRNA 1729	1729	TTTCAATAAACCTTTTGTT	3471	AACAAAAGGTTTATTGAAA
siRNA 1730	1730	TTCAATAAACCTTTTGTTT	3472	AAACAAAAGGTTTATTGAA
siRNA 1731	1731	TCAATAAACCTTTTGTTTC	3473	GAAACAAAAGGTTTATTGA
siRNA 1732	1732	CAATAAACCTTTTGTTTCC	3474	GGAAACAAAAGGTTTATTG
siRNA 1733	1733	AATAAACCTTTTGTTTCCT	3475	AGGAAACAAAAGGTTTATT
siRNA 1734	1734	ATAAACCTTTTGTTTCCTA	3476	TAGGAAACAAAAGGTTTAT
siRNA 1735	1735	TAAACCTTTTGTTTCCTAA	3477	TTAGGAAACAAAAGGTTTA
siRNA 1736	1736	AAACCTTTTGTTTCCTAAG	3478	CTTAGGAAACAAAAGGTTT
siRNA 1737	1737	AACCTTTTGTTTCCTAAGA	3479	TCTTAGGAAACAAAAGGTT
siRNA 1738	1738	ACCTTTTGTTTCCTAAGAC	3480	GTCTTAGGAAACAAAAGGT
siRNA 1739	1739	CCTTTTGTTTCCTAAGACT	3481	AGTCTTAGGAAACAAAAGG
siRNA 1740	1740	CTTTTGTTTCCTAAGACTA	3482	TAGTCTTAGGAAACAAAAG
siRNA 1741	1741	TTTGTTTCCTAAGACTAG	3483	CTAGTCTTAGGAAACAAA
siRNA 1742	1742	TTTGTTTCCTAAGACTAGA	3484	TCTAGTCTTAGGAAACAAA

Table 80. Additional Sequences

SEQ ID NO:	5' to 3' Sequence
3621	AAAAAGGAGGAGCTTCAACCTGTGTGCAAAATCTGGGAACCTGACAGTATAGGTTG GGGGCCAGGATGAGGAAAAAGGAACGGGAAAGACCTGCCACCTTCCTGGTAAGG AGGCCCCGTGATCAGCTCCAGCCATTTGCAGTCCTGGCTATCCCAGGAGCTTACATA AAGGGACAATTGGAGCCTGAGAGGTGACAGTGCTGACACTACAAGGCTCGGAGCT CCGGGCACTCAGACATCATGAGTTGGTCTTGACACCCCGGAATTTAATCTCTACT TCTATGCTCTTTTATTTCTCTCTCAACATGTGTAGCATATGTTGCTACAGAGACAA CTGCTGCATCTTAGATGAAAGATTTCGGTAGTTATTGTCCAACCTGTGGCATTGC AGATTTCTGTCTACTTATCAAACCAAAGTAGACAAGGATCTACAGTCTTTGGAAG ACATCTTACATCAAGTTGAAAACAAAACATCAGAAGTCAAACAGCTGATAAAAGC

SEQ ID NO:	5' to 3' Sequence
	AATCCAACCTCACTTATAATCCTGATGAATCATCAAAACCAAATATGATAGACGCTG CTACTTTGAAGTCCAGGAAAATGTTAGAAGAAATTATGAAATATGAAGCATCGATT TTAACACATGACTCAAGTATTCGATATTTGCAGGAAATATATAATTCAAATAATCA AAAGATTGTTAACCTGAAAGAGAAGGTAGCCCAGCTTGAAGCACAGTGCCAGGAA CCTTGCAAAGACACGGTGCAAATCCATGATATCACTGGGAAAAGATTGTCAAGACAT TGCCAATAAGGGAGCTAAACAGAGCGGGCTTTACTTTATTAACCTCTGAAAGCTA ACCGCAATTCTTAGTCTACTGTGAAATCGATGGGTCTGGAAATGGATGGACTGTG TTTCAGAAGAGACTTGATGGCAGTGTAGATTTCAAGAAAACTGGATTCAATATAA AGAAGGATTTGGACATCTGTCTCCTACTGGCACAACAGAATTTTGGCTGGGAAATG AGAAGATTCATTTGATAAGCACACAGTCTGCCATCCCATATGCATTAAGAGTGGAA CTGGAAGACTGGAATGGCAGAACCAGTACTGCAGACTATGCCATGTTCAAGGTGGG ACCTGAAGCTGACAAGTACCGCCTAACATATGCCTACTTCGCTGGTGGGGATGCTG GAGATGCCTTTGATGGCTTTGATTTTGGCGATGATCCTAGTGACAAGTTTTTCACAT CCCATAATGGCATGCAGTTCAGTACCTGGGACAATGACAATGATAAGTTTGAAGGC AACTGTGCTGAACAGGATGGATCTGGTTGGTGGATGAACAAGTGTACGCTGGCCA TCTCAATGGAGTTTATTACCAAGGTGGCACTTACTCAAAGCATCTACTCCTAATGG TTATGATAATGGCATTATTTGGGCCACTTGGAAAACCGGTGGTATTCCATGAAGA AAACCACTATGAAGATAATCCCATTCACAGACTCACAATTGGAGAAGGACAGCA ACACCACCTGGGGGGAGCCAAACAGGCTGGAGACGTTTAAAAGACCGTTTCAAAA GAGATTTACTTTTTTAAAGGACTTTATCTGAACAGAGAGATATAATATTTTCTAT TGGACAATGGACTTGCAAAGCTTCACTTCATTTAAGAGCAAAAGACCCCATGTTG AAAACCTCCATAACAGTTTTATGCTGATGATAATTTATCTACATGCATTTCAATAAAC CTTTTGTTCCTAAGACTAGA
3622	NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3623	nsnsnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3624	nsnsnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3625	NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsnN-moiety (e.g. a sugar moiety)
3626	nsnsnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsnN-moiety (e.g. sugar moiety)
3627	NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3628	nsnsnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3629	nsnsnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3630	nsnsnnnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3631	nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3632	nsNfsnnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3633	nsNfsnnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3634	nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3635	nsNfsnnnnnnnnnnnnNfnNfnNfnNfnNfnNfsnsn
3636	nsNfsnnnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3637	nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3638	nsNfsnnnnnnnnnnnnNfnNfnNfnNfnNfnNfsnsn
3639	nNfnNfnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn
3640	nsnsnsnsnsdNsdNsdNsdNsdNsdNsdNsdNsdNsdNsdNsdNfsnsnsnsn

Table 81. Modified siRNA Sequences

siRNA Name	SEQ ID NO:	Sense strand sequence (5'-3')	SEQ ID NO:	Antisense strand sequence (5'-3')
siRNA 3599	3599	[ETL1]gsasugaAfaGfAfuucgguaguasusu	3595	usApscUfaCfcGfaAfuCfuUfuCfaUfcsusu
siRNA 3600	3600	[ETL1]gsasugaAfaGfAfuucgguaguasusu	3595	usApscUfaCfcGfaAfuCfuUfuCfaUfcsusu
siRNA 3601	3601	[ETL1]gsasugaAfaGfAfuucgguaguasusu	3595	usApscUfaCfcGfaAfuCfuUfuCfaUfcsusu
siRNA 3602	3602	[ETL1]gsasugAfaaGfAfuucgguaguasusu	3595	usApscUfaCfcGfaAfuCfuUfuCfaUfcsusu
siRNA 3603	3603	[ETL1]gsasugAfaAfgAfuucgguaguasusu	3595	usApscUfaCfcGfaAfuCfuUfuCfaUfcsusu

siRNA 3604	3604	[ETL1]gsasugAfAfagAfuucgguaguasusu	3595	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
ETD01592	3591	[ETL1]gsasugAfAfagAfuucgguaguasusu	3595	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
siRNA 3605	3605	[ETL1]gsasugAfAfAfGfAfuucgguaguasusu	3595	usAfscUfaCfcGfaAfuCfuUfuCfaUfcsusu
siRNA 3606	3606	[ETL1]gsgsaaaugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3607	3607	[ETL1]gsgsaaaugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3608	3608	[ETL1]gsgsaaaGfAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
ETD01593	3592	[ETL1]gsgsaaaGfAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3609	3609	[ETL1]gsgsaaaGfAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3610	3610	[ETL1]gsgsaaaGfAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3611	3611	[ETL1]gsgsaaAfugaGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3612	3612	[ETL1]gsgsaaAfugaGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3613	3613	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3614	3614	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3615	3615	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3616	3616	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3617	3617	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3618	3618	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
siRNA 3619	3619	[ETL1]gsgsaaAfugAfGfAfagauucauasusu	3596	usAfsuGfaAfuCfuUfcUfcAfuUfuCfcsusu
ETD01594	3593	[ETL1]gsasagAfuucAfuugauaagasusu	3597	usCfsuUfaUfcAfaAfuGfaAfuCfuUfcsusu
siRNA 3620	3620	[ETL1]usasaguuuGfAfAfGfgcaacugasusu	3598	usCfsaGfuUfgCfcUfuCfaAfaCfuUfasusu
ETD01595	3594	[ETL1]usasaguuuGfAfAfGfgcaacugasusu	3598	usCfsaGfuUfgCfcUfuCfaAfaCfuUfasusu

[ETL1] = GalNAc#1 (shown connected 5' to the sense strand)

CLAIMS

What is claimed is:

1. A composition comprising an oligonucleotide that targets FGG and when administered to a subject in an effective amount improves a mental disorder measurement in the subject, relative to a baseline mental disorder measurement.
2. The composition of claim 1, wherein the mental disorder comprises a psychiatric disorder.
3. The composition of claim 2, wherein the psychiatric disorder comprises a depressive disorder, post-traumatic stress disorder, mood disorder, anxiety disorder, eating disorder, substance-use disorder, bipolar disorder, personality disorder, schizophrenia, or schizoaffective disorder.
4. The composition of claim 1, wherein the mental disorder measurement comprises a Montgomery-Asberg Depression Rating Scale score, a Hamilton Depression Rating Scale score, or a measurement of an anxiety disorder, depressive disorder, eating disorder, substance-use disorder, post-traumatic stress disorder, bipolar disorder, schizophrenia, or psychosis sign or symptom.
5. The composition of claim 1, wherein the mental disorder comprises a neurological disorder.
6. The composition of claim 5, wherein the neurological disorder comprises Alzheimer's disease, dementia, delirium, cognitive decline, vascular dementia, headache, chronic pain, chronic fatigue syndrome, or motor neuron disease.
7. The composition of claim 6, wherein the mental disorder measurement comprises a measurement of cognitive function, CNS amyloid plaques, CNS tau accumulation, CSF beta-amyloid 42, CSF tau, CSF phospho-tau, Lewy bodies, CSF alpha-synuclein, or a sign or symptom of headache, migraine, chronic pain, fibromyalgia, chronic fatigue syndrome, or motor neuron disease.
8. A composition comprising an oligonucleotide that targets FGG and when administered to a subject in an effective amount decreases fibrinogen.
9. The composition of claim 8, wherein the composition decreases circulating fibrinogen.
10. The composition of claim 8, wherein the subject has a clotting or coagulation disorder.
11. The composition of claim 8, wherein the subject has a thrombophilia.
12. The composition of claim 8, wherein the subject has a venous thromboembolism.
13. The composition of any one of the preceding claims, wherein the oligonucleotide comprises a modified internucleoside linkage.
14. The composition of claim 13, wherein the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof.
15. The composition of claim 13, wherein the modified internucleoside linkage comprises one or more phosphorothioate linkages.
16. The composition of any one of the preceding claims, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages.

17. The composition of any one of the preceding claims, wherein the oligonucleotide comprises a modified nucleoside.

18. The composition of claim 17, wherein the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof.

19. The composition of claim 17, wherein the modified nucleoside comprises a LNA.

20. The composition of claim 17, wherein the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid.

21. The composition of claim 17, wherein the modified nucleoside comprises 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof.

22. The composition of claim 17, wherein the modified nucleoside comprises one or more 2' fluoro modified nucleosides.

23. The composition of claim 17, wherein the modified nucleoside comprises 2' O-alkyl modified nucleoside.

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

25. The composition of any one of the preceding claims, wherein the oligonucleotide comprises a sugar moiety attached at a 3' or 5' terminus of the oligonucleotide.

26. The composition of claim 25, wherein the sugar comprises N-acetylgalactosamine (GalNAc), N-acetylglucosamine (GlcNAc), or mannose.

27. The composition of claim 25, wherein the sugar comprises GalNAc.

28. The composition of claim 27, wherein the sugar moiety comprises ETL17.

29. The composition of any one of the preceding claims, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand.

30. The composition of claim 29, wherein the sense strand is 12-30 nucleosides in length.

31. The composition of claim 29, wherein the antisense strand is 12-30 nucleosides in length.

32. A composition comprising an oligonucleotide that inhibits the expression of FG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 3621.

33. The composition of claim 29, wherein any one of the following is true with regard to the sense strand:

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

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

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

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

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

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

34. The composition of claim 29, wherein the antisense strand comprises a mixture of 2' fluoro and 2'-O-methyl modified nucleosides.

35. The composition of claim 1 or 8, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO).

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

37. A composition comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and a nucleoside sequence complementary to about 12-30 contiguous nucleosides of SEQ ID NO: 3621.

38. The composition of any one of claims 1-37, further comprising a pharmaceutically acceptable carrier.

39. A method of treating a subject having a psychiatric disorder or a neurological disorder, comprising administering an effective amount of the composition of claim 38 to the subject.

40. The method of claim 39, wherein the psychiatric disorder comprises a depressive disorder, persistent depressive disorder, treatment resistant depression, a sign or symptom of depression, post-traumatic stress disorder, mood disorder, anxiety disorders, eating disorder, substance-use disorder, bipolar disorder, personality disorder, schizophrenia, or a schizoaffective disorder.

41. The method of claim 39, wherein the neurological disorder comprises Alzheimer's disease, dementia, delirium, cognitive decline, vascular dementia, headache, chronic pain, chronic fatigue syndrome, and motor neuron disease.

42. A method of treating a subject having a clotting or coagulation disorder or a thrombophilia, comprising administering an effective amount of the composition of claim 38 to the subject.

43. The method of claim 42, wherein the prothrombin time, International Normalized Ratio, or the activated partial thromboplastin time is increased compared to a baseline.