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(54) **COMPOSITIONS FOR MODULATING C9ORF72 EXPRESSION**

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(57) **ABSTRACT**

Disclosed herein are compositions and methods for reducing expression of C9ORF72 mRNA and protein in an animal with C9ORF72 specific inhibitors. Such methods are useful to treat, prevent, or ameliorate neurodegenerative diseases in an individual in need thereof. Such C9ORF72 specific inhibitors include antisense compounds. Examples of neurodegenerative diseases that can be treated, prevented, and ameliorated with the administration C9ORF72 specific inhibitors include amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticalbasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, and olivopontocerellar degeneration (OPCD).

Specification includes a Sequence Listing.

COMPOSITIONS FOR MODULATING C9ORF72 EXPRESSION

SEQUENCE LISTING

[0001] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0211USC1SEQ.txt created Aug. 17, 2019, which is 184 Kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD

[0002] Provided are compositions and methods for reducing expression of C9ORF72 mRNA and protein in an animal. Such methods are useful to treat, prevent, or ameliorate neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticalbasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, and olivopontocerellar degeneration (OPCD).

BACKGROUND

[0003] Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized clinically by progressive paralysis leading to death from respiratory failure, typically within two to three years of symptom onset (Rowland and Shneider, N. Engl. J. Med., 2001, 344, 1688-1700). ALS is the third most common neurodegenerative disease in the Western world (Hirtz et al., Neurology, 2007, 68, 326-337), and there are currently no effective therapies. Approximately 10% of cases are familial in nature, whereas the bulk of patients diagnosed with the disease are classified as sporadic as they appear to occur randomly throughout the population (Chio et al., Neurology, 2008, 70, 533-537). There is growing recognition, based on clinical, genetic, and epidemiological data, that ALS and frontotemporal dementia (FTD) represent an overlapping continuum of disease, characterized pathologically by the presence of TDP-43 positive inclusions throughout the central nervous system (Lillo and Hodges, J. Clin. Neurosci., 2009, 16, 1131-1135; Neumann et al., Science, 2006, 314, 130-133).

[0004] To date, a number of genes have been discovered as causative for classical familial ALS, for example, SOD1, TARDBP, FUS, OPTN, and VCP (Johnson et al., Neuron, 2010, 68, 857-864; Kwiatkowski et al., Science, 2009, 323, 1205-1208; Maruyama et al., Nature, 2010, 465, 223-226; Rosen et al., Nature, 1993, 362, 59-62; Sreedharan et al., Science, 2008, 319, 1668-1672; Vance et al., Brain, 2009, 129, 868-876). Recently, linkage analysis of kindreds involving multiple cases of ALS, FTD, and ALS-FTD had suggested that there was an important locus for the disease on the short arm of chromosome 9 (Boxer et al., J. Neurol. Neurosurg. Psychiatry, 2011, 82, 196-203; Morita et al., Neurology, 2006, 66, 839-844; Pearson et al. J. Nerol., 2011, 258, 647-655; Vance et al., Brain, 2006, 129, 868-876). The chromosome 9p21ALS-FTD locus in the last major autosomal-dominant gene whose mutation is causative of ALS. The ALS-FTD causing mutation is a large hexanucleotide (GGGGCC) repeat expansion in the first intron of the C9ORF72 gene (Renton et al., Neuron, 2011, 72, 257-268; DeJesus-Hernandez et al., Neuron, 2011, 72, 245-256). A founder haplotype, covering the C9ORF72 gene, is present in the majority of cases linked to this region (Renton et al., Neuron, 2011, 72, 257-268). This locus on chromosome 9p21 accounts for nearly half of familial ALS and nearly one-quarter of all ALS cases in a cohort of 405 Finnish patients (Laaksovirta et al, Lancet Neurol., 2010, 9, 978-985).

[0005] A founder haplotype, covering the C9ORF72 gene, is present in the majority of cases linked to this region.

[0006] There are currently no effective therapies to treat such neurodegenerative diseases. Therefore, it is an object to provide compositions and methods for the treatment of such neurodegenerative diseases.

SUMMARY

[0007] Provided herein are compositions and methods for modulating levels of C9ORF72 mRNA and protein in cells, tissues, and animals. In certain embodiments, C9ORF72 specific inhibitors modulate expression of C9ORF72 mRNA and protein. In certain embodiments, C9ORF72 specific inhibitors are nucleic acids, proteins, or small molecules.

[0008] In certain embodiments, modulation can occur in a cell or tissue. In certain embodiments, the cell or tissue is in an animal. In certain embodiments, the animal is a human. In certain embodiments, C9ORF72 mRNA levels are reduced. In certain embodiments, C9ORF72 protein levels are reduced. In certain embodiments, certain C9ORF72 mRNA variants are preferentially reduced. In certain embodiments, the C9ORF72 mRNA variants preferentially reduced are variants containing intron 1. In certain embodiments, intron 1 contains a hexanucleotide repeat expansion. In certain embodiments, the hexanucleotide repeat expansion is associated with a C9ORF72 associated disease. In certain embodiments, the hexanucleotide repeat expansion is associated with a C9ORF72 hexanucleotide repeat expansion associated disease. In certain embodiments, the hexanucleotide repeat expansion comprises at least 30 GGGGCC repeats. In certain embodiments, the hexanucleotide repeat expansion is associated with nuclear foci. In certain embodiments, the compositions and methods described herein are useful for reducing C9ORF72 mRNA levels, C9ORF72 protein levels, and nuclear foci. Such reduction can occur in a time-dependent manner or in a dose-dependent manner.

[0009] Also provided are methods useful for preventing, treating, and ameliorating diseases, disorders, and conditions associated with C9ORF72. In certain embodiments, such diseases, disorders, and conditions associated with C9ORF72 are neurodegenerative diseases. In certain embodiments, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), corticalbasal degeneration syndrome (CBD), atypical Parkinsonian syndrome, and olivopontocerellar degeneration (OPCD).

[0010] Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a neurodegenerative disease, and, in particular, ALS and FTD, include genetic predisposition and older age.

[0011] In certain embodiments, methods of treatment include administering a C9ORF72 specific inhibitor to an individual in need thereof. In certain embodiments, the C9ORF72 specific inhibitor is a nucleic acid. In certain embodiments, the nucleic acid is an antisense compound. In certain embodiments, the antisense compound is a single-stranded antisense oligonucleotide. In certain embodiments,

the single-stranded antisense oligonucleotide is complementary to a C9ORF72 nucleic acid.

DETAILED DESCRIPTION

[0012] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Additionally, as used herein, the use of "and" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

[0013] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this disclosure, including, but not limited to, patents, patent applications, published patent applications, articles, books, treatises, and GENBANK Accession Numbers and associated sequence information obtainable through databases such as National Center for Biotechnology Information (NCBI) and other data referred to throughout in the disclosure herein are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

Definitions

[0014] Unless specific definitions are provided, the nomenclature utilized in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, and chemical analysis.

[0015] Unless otherwise indicated, the following terms have the following meanings:

[0016] "2'-O-methoxyethyl group" (also 2'-MOE and 2'-OCH_2CH_2—OCH_3 and MOE) refers to an O-methoxyethyl modification of the 2' position of a furanosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

[0017] "2'-MOE nucleoside" (also 2'-O-methoxyethyl nucleoside) means a nucleoside comprising a 2'-O-methoxyethyl group.

[0018] "5-methylcytosine" means a cytosine modified with a methyl group attached to the 5' position. A 5-methylcytosine is a modified nucleobase.

[0019] "About" means within ±7% of a value. For example, if it is stated, "the compounds affected at least about 70% inhibition of C9ORF72", it is implied that the C9ORF72 levels are inhibited within a range of 63% and 77%.

[0020] "Administered concomitantly" refers to the co-administration of two pharmaceutical agents in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Concomitant administration does not require that both pharmaceutical agents be administered in a single pharmaceutical composition, in the same dosage form, or by the same route of administration. The effects of both pharmaceutical agents need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive.

[0021] "Administering" means providing a pharmaceutical agent to an animal, and includes, but is not limited to administering by a medical professional and self-administering.

[0022] "Amelioration" or "ameliorate" or "ameliorating" refers to a lessening of at least one indicator, sign, or symptom of a disease, disorder, or condition. The severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

[0023] "Animal" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

[0024] "Antibody" refers to a molecule characterized by reacting specifically with an antigen in some way, where the antibody and the antigen are each defined in terms of the other. Antibody may refer to a complete antibody molecule or any fragment or region thereof, such as the heavy chain, the light chain, Fab region, and Fc region.

[0025] "Antisense activity" means any detectable or measurable activity attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid.

[0026] "Antisense compound" means an oligomeric compound that is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding. Examples of antisense compounds include single-stranded and double-stranded compounds, such as, antisense oligonucleotides, siRNAs, shRNAs, ssRNAs, and occupancy-based compounds. Antisense mechanisms include, without limitation, RNase H mediated antisense; RNAi mechanisms, which utilize the RISC pathway and include, without limitation, siRNA, ssRNA and microRNA mechanisms; and occupancy based mechanisms, including, without limitiation uniform modified oligonucleotides. Certain antisense compounds may act through more than one such mechanism and/or through additional mechanisms.

[0027] "Antisense inhibition" means reduction of target nucleic acid levels or target protein levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound. Inhibition may be any means including RNase H degradation, such as with a gapmer, and steric blockage, such as with a uniformly modified oligonucleotide.

[0028] "Antisense oligonucleotide" means a single-stranded oligonucleotide having a nucleobase sequence that permits hybridization to a corresponding segment of a target nucleic acid.

[0029] "Bicyclic sugar" means a furanosyl ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

[0030] "Bicyclic nucleoside" (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

[0031] "C9ORF72 associated disease" means any disease associated with any C9ORF72 nucleic acid or expression product thereof. Such diseases may include a neurodegenerative disease. Such neurodegenerative diseases may include ALS and FTD.

[0032] "C9ORF72 hexanucleotide repeat expansion associated disease" means any disease associated with a C9ORF72 nucleic acid containing a hexanucleotide repeat expansion. In certain embodiments, the hexanucleotide repeat expansion may comprise GGGGCC, GGGGGG, GGGGGC, or GGGGCG repeated at least 30 times. Such diseases may include a neurodegenerative disease. Such neurodegenerative diseases may include ALS and FTD.

[0033] "C9ORF72 nucleic acid" means any nucleic acid encoding C9ORF72. For example, in certain embodiments, a C9ORF72 nucleic acid includes a DNA sequence encoding C9ORF72, an RNA sequence transcribed from DNA encoding C9ORF72 (including genomic DNA comprising introns and exons), and an mRNA sequence encoding C9ORF72. "C9ORF72 mRNA" means an mRNA encoding a C9ORF72 protein.

[0034] "C9ORF72 specific inhibitor" refers to any agent capable of specifically inhibiting the expression of C9ORF72 mRNA and/or C9ORF72 protein at the molecular level. For example, C9ORF72 specific inhibitors include nucleic acids (including antisense compounds), siRNAs, aptamers, antibodies, peptides, small molecules, and other agents capable of inhibiting the expression of C9ORF72 mRNA and/or C9ORF72 protein. Similarly, in certain embodiments, C9ORF72 specific inhibitors may affect other molecular processes in an animal.

[0035] "Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

[0036] "cEt" or "constrained ethyl" means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-$CH(CH_3)$—O-2'.

[0037] "Constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-$CH(CH_3)$—O-2' bridge.

[0038] "Chemically distinct region" refers to a region of an antisense compound that is in some way chemically different than another region of the same antisense compound. For example, a region having 2'-O-methoxyethyl nucleosides is chemically distinct from a region having nucleosides without 2'-O-methoxyethyl modifications.

[0039] "Chimeric antisense compound" means an antisense compound that has at least two chemically distinct regions.

[0040] "Co-administration" means administration of two or more pharmaceutical agents to an individual. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration encompasses parallel or sequential administration.

[0041] "Complementarity" means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

[0042] "Contiguous nucleobases" means nucleobases immediately adjacent to each other.

[0043] "Diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, the diluent in an injected composition may be a liquid, e.g. saline solution.

[0044] "Dose" means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose may be administered in one, two, or more boluses, tablets, or injections. For example, in certain embodiments where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection, therefore, two or more injections may be used to achieve the desired dose. In certain embodiments, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses may be stated as the amount of pharmaceutical agent per hour, day, week, or month.

[0045] "Effective amount" means the amount of pharmaceutical agent sufficient to effectuate a desired physiological outcome in an individual in need of the pharmaceutical agent. The effective amount may vary among individuals depending on the health and physical condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual's medical condition, and other relevant factors.

[0046] "Expression" means conversion of the information from a C9ORF72 gene into mRNA via transcription and then to protein via translation. Expression may result in a phenotypic manifestation of the C9ORF72 gene.

[0047] "Fully complementary" or "100% complementary" means each nucleobase of a first nucleic acid has a complementary nucleobase in a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a target nucleic acid is a second nucleic acid.

[0048] "Gapmer" means a chimeric antisense compound in which an internal region having a plurality of nucleosides that support RNase H cleavage is positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as a "gap" and the external regions may be referred to as the "wings."

[0049] "Gap-narrowed" means a chimeric antisense compound having a gap segment of 9 or fewer contiguous 2'-deoxyribonucleosides positioned between and immediately adjacent to 5' and 3' wing segments having from 1 to 6 nucleosides.

[0050] "Gap-widened" means a chimeric antisense compound having a gap segment of 12 or more contiguous 2'-deoxyribonucleosides positioned between and immediately adjacent to 5' and 3' wing segments having from 1 to 6 nucleosides.

[0051] "Hexanucleotide repeat expansion" means a series of six bases (for example, GGGGCC, GGGGGG, GGGGCG, or GGGGGC) repeated at least twice. In certain embodiments, the hexanucleotide repeat expansion may be located in intron 1 of a C9ORF72 nucleic acid. In certain embodiments, a pathogenic hexanucleotide repeat expansion includes at least 30 repeats of GGGGCC, GGGGGG, GGGGCG, or GGGGGC in a C9ORF72 nucleic acid and is associated with disease. In certain embodiments, the repeats are consecutive. In certain embodiments, the repeats are

interrupted by 1 or more nucleobases. In certain embodiments, a wild-type hexanucleotide repeat expansion includes 23 or fewer repeats of GGGGCC, GGGGGG, GGGGCG, or GGGGGC in a C9ORF72 nucleic acid. In certain embodiments, the repeats are consecutive. In certain embodiments, the repeats are interrupted by 1 or more nucleobases.

[0052] "Hybridization" means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include an antisense compound and a target nucleic acid.

[0053] "Identifying an animal having a C9ORF72 associated disease" means identifying an animal having been diagnosed with a C9ORF72 associated disease or predisposed to develop a C9ORF72 associated disease. Individuals predisposed to develop a C9ORF72 associated disease include those having one or more risk factors for developing a C9ORF72 associated disease, including, having a personal or family history or genetic predisposition of one or more C9ORF72 associated diseases. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments, such as genetic testing.

[0054] "Immediately adjacent" means there are no intervening elements between the immediately adjacent elements.

[0055] "Individual" means a human or non-human animal selected for treatment or therapy.

[0056] "Inhibiting C9ORF72" means reducing expression of C9ORF72 mRNA and/or protein levels in the presence of a C9ORF72 specific inhibitor, including a C9ORF72 antisense oligonucleotide, as compared to expression of C9ORF72 mRNA and/or protein levels in the absence of a C9ORF72 specific inhibitor, such as a C9ORF72 antisense oligonucleotide.

[0057] "Internucleoside linkage" refers to the chemical bond between nucleosides.

[0058] "Linked nucleosides" means adjacent nucleosides which are bonded together.

[0059] "Mismatch" or "non-complementary nucleobase" refers to the case when a nucleobase of a first nucleic acid is not capable of pairing with the corresponding nucleobase of a second or target nucleic acid.

[0060] "Modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside bond (i.e., a phosphodiester internucleoside bond).

[0061] "Modified nucleobase" refers to any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[0062] "Modified nucleotide" means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, or modified nucleobase. A "modified nucleoside" means a nucleoside having, independently, a modified sugar moiety or modified nucleobase.

[0063] "Modified oligonucleotide" means an oligonucleotide comprising a modified internucleoside linkage, a modified sugar, or a modified nucleobase.

[0064] "Modified sugar" refers to a substitution or change from a natural sugar.

[0065] "Motif" means the pattern of chemically distinct regions in an antisense compound.

[0066] "Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[0067] "Natural sugar moiety" means a sugar found in DNA (2'-H) or RNA (2'-OH).

[0068] "Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, small interfering ribonucleic acids (siRNA), and microRNAs (miRNA).

[0069] "Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

[0070] "Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, or nucleobase modification.

[0071] "Nucleoside" means a nucleobase linked to a sugar.

[0072] "Nucleoside mimetic" includes those structures used to replace the sugar or the sugar and the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo, or tricyclo sugar mimetics, e.g., non furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by —N(H)—C(═O)—O— or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system.

[0073] "Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[0074] "Oligomeric compound" or "oligomer" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

[0075] "Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

[0076] "Parenteral administration" means administration through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g., intrathecal or intracerebroventricular administration.

[0077] "Peptide" means a molecule formed by linking at least two amino acids by amide bonds. Peptide refers to polypeptides and proteins.

[0078] "Pharmaceutical agent" means the substance or substances in a pharmaceutical composition that provide a therapeutic benefit when administered to an individual. For example, in certain embodiments an antisense oligonucleotide targeted to C9ORF72 is a pharmaceutical agent.

[0079] "Pharmaceutical composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition may comprise one or more pharmaceutical agents and a sterile aqueous solution.

[0080] "Pharmaceutically acceptable derivative" encompasses pharmaceutically acceptable salts, conjugates, prodrugs or isomers of the compounds described herein.

[0081] "Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

[0082] "Phosphorothioate linkage" means a linkage between nucleosides where the phosphodiester bond is modified by replacing one of the non-bridging oxygen atoms with a sulfur atom. A phosphorothioate linkage (P═S) is a modified internucleoside linkage.

[0083] "Portion" means a defined number of contiguous (i.e., linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an antisense compound.

[0084] "Prevent" or "preventing" refers to delaying or forestalling the onset or development of a disease, disorder, or condition for a period of time from minutes to indefinitely. Prevent also means reducing risk of developing a disease, disorder, or condition.

[0085] "Prodrug" means a therapeutic agent that is prepared in an inactive form that is converted to an active form within the body or cells thereof by the action of endogenous enzymes or other chemicals or conditions.

[0086] "Side effects" means physiological responses attributable to a treatment other than the desired effects. In certain embodiments, side effects include injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, myopathies, and malaise.

[0087] "Single-stranded oligonucleotide" means an oligonucleotide which is not hybridized to a complementary strand.

[0088] "Specifically hybridizable" refers to an antisense compound having a sufficient degree of complementarity between an antisense oligonucleotide and a target nucleic acid to induce a desired effect, while exhibiting minimal or no effects on non-target nucleic acids under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays and therapeutic treatments.

[0089] "Targeting" or "targeted" means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

[0090] "Target nucleic acid," "target RNA," and "target RNA transcript" all refer to a nucleic acid capable of being targeted by antisense compounds.

[0091] "Target segment" means the sequence of nucleotides of a target nucleic acid to which an antisense compound is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment.

[0092] "Therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

[0093] "Treat" or "treating" refers to administering a pharmaceutical composition to effect an alteration or improvement of a disease, disorder, or condition.

[0094] "Unmodified nucleotide" means a nucleotide composed of naturally occurring nucleobases, sugar moieties, and internucleoside linkages. In certain embodiments, an unmodified nucleotide is an RNA nucleotide (i.e. β-D-ribonucleosides) or a DNA nucleotide (i.e. β-D-deoxyribonucleoside).

Certain Embodiments

[0095] Certain embodiments provide methods for decreasing C9ORF72 mRNA and protein expression.

[0096] Certain embodiments provide methods for the treatment, prevention, or amelioration of diseases, disorders, and conditions associated with C9ORF72 in an individual in need thereof. Also contemplated are methods for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with C9ORF72. C9ORF72 associated diseases, disorders, and conditions include neurodegenerative diseases. In certain embodiments, the neurodegenerative disease may be ALS or FTD. In certain embodiments, the neurodegenerative disease may be familial or sporadic.

[0097] Certain embodiments provide for the use of a C9ORF72 specific inhibitor for treating, preventing, or ameliorating a C9ORF72 associated disease. Certain embodiments provide for the use of a C9ORF72 specific inhibitor for treating, preventing, or ameliorating a C9ORF72 hexanucleotide repeat expansion associated disease. In certain embodiments, the hexanucleotide repeat expansion may comprise GGGGCC, GGGGGG, GGGGGC, or GGGGCG. In certain embodiments, C9ORF72 specific inhibitors are nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of C9ORF72 mRNA and/or C9ORF72 protein.

[0098] Described herein are compounds comprising a single-stranded antisense oligonucleotide complementary to a C9ORF72 nucleic acid or a C9ORF72 homolog nucleic acid.

[0099] In certain embodiments, the C9ORF72 nucleic acid is a human C9ORF72 nucleic acid.

[0100] In certain embodiments, the C9ORF72 nucleic acid contains a hexanucleotide repeat expansion.

[0101] In certain embodiments, the C9ORF72 nucleic acid does not contain a hexanucleotide repeat expansion.

[0102] In certain embodiments, the single-stranded antisense oligonucleotide is specifically hybridizable to a human C9ORF72 nucleic acid.

[0103] In certain embodiments, the single-stranded antisense oligonucleotide is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of a human C9ORF72 nucleic acid.

[0104] In certain embodiments, the single-stranded antisense oligonucleotide is complementary to any of exon, an intron, the 5' UTR, the 3' UTR, a repeat region, a splice junction, an exon:exon splice junction, an exonic splicing silencer (ESS), an exonic splicing enhancer (ESE), exon 1a, exon 1b, exon 1c, exon 1d, exon 1e, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, intron 1, intron 2, intron 3, intron 4, intron 5, intron 6, intron 7, intron 8, intron 9, or intron 10 of a human C9ORF72 nucleic acid.

[0105] Described herein are compounds comprising a single-stranded antisense oligonucleotide consisting of 12 to 30 linked nucleosides and comprising a nucleobase

sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of SEQ ID NO: 30-369.

[0106] In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modification.

[0107] In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified internucleoside linkage.

[0108] In certain embodiments, each internucleoside linkage of the single-stranded antisense oligonucleotide is a modified internucleoside linkage.

[0109] In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

[0110] In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleoside.

[0111] In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleoside having a modified sugar.

[0112] In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar.

[0113] In certain embodiments, the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-$(CH_2)_n$—O-2' bridge, wherein n is 1 or 2; and 4'-CH_2—O—CH_2-2'.

[0114] In certain embodiments, the bicyclic sugar comprises a 4'-$CH(CH_3)$—O-2' bridge.

[0115] In certain embodiments, the at least one modified nucleoside having a modified sugar comprises a non-bicyclic 2'-modified modified sugar moiety.

[0116] In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methoxyethyl group.

[0117] In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methyl group.

[0118] In certain embodiments, the at least one modified nucleoside having a modified sugar comprises a sugar surrogate.

[0119] In certain embodiments, the sugar surrogate is a morpholino.

[0120] In certain embodiments, the sugar surrogate is a peptide nucleic acid.

[0121] In certain embodiments, each nucleoside is modified.

[0122] In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleobase.

[0123] In certain embodiments, the modified nucleobase is a 5'-methylcytosine.

[0124] In certain embodiments, the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides;

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

[0125] In certain embodiments, the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides;

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned immediately adjacent and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

[0126] In certain embodiments, the single-stranded antisense oligonucleotide consists of 15 linked nucleosides.

[0127] In certain embodiments, the single-stranded antisense oligonucleotide consists of 16 linked nucleosides.

[0128] In certain embodiments, the single-stranded antisense oligonucleotide consists of 17 linked nucleosides.

[0129] In certain embodiments, the single-stranded antisense oligonucleotide consists of 18 linked nucleosides.

[0130] In certain embodiments, the single-stranded antisense oligonucleotide consists of 19 linked nucleosides.

[0131] In certain embodiments, the single-stranded antisense oligonucleotide consists of 20 linked nucleosides.

[0132] In certain embodiments, the single-stranded antisense oligonucleotide consists of 21 linked nucleosides.

[0133] In certain embodiments, the single-stranded antisense oligonucleotide consists of 22 linked nucleosides.

[0134] In certain embodiments, the single-stranded antisense oligonucleotide consists of 23 linked nucleosides.

[0135] In certain embodiments, the single-stranded antisense oligonucleotide consists of 24 linked nucleosides.

[0136] In certain embodiments, the single-stranded antisense oligonucleotide consists of 25 linked nucleosides.

[0137] Described herein are uses of the compound for the manufacture of a medicament for treating a neurodegenerative disease.

[0138] Provided herein are methods of preferentially inhibiting expression of mRNA transcripts containing a hexanucleotide repeat expansion by contacting a cell with an antisense oligonucleotide targeting upstream of exon 1B.

Antisense Compounds

[0139] Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, and siRNAs. An oligomeric compound may be "antisense" to a target nucleic acid, meaning that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

[0140] In certain embodiments, an antisense compound has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted. In certain such embodiments, an antisense oligonucleotide has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted.

[0141] In certain embodiments, an antisense compound targeted to a C9ORF72 nucleic acid is 12 to 30 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits. In certain embodiments, the antisense compound is 8 to 80, 12 to 50, 15 to 30, 18 to 24, 19 to 22, or 20 linked subunits. In certain embodiments, the antisense compounds are 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, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 linked subunits in length, or a range defined by any two of

the above values. In some embodiments the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleosides.

[0142] In certain embodiments antisense oligonucleotides targeted to a C9ORF72 nucleic acid may be shortened or truncated. For example, a single subunit may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated antisense compound targeted to a C9ORF72 nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the antisense compound. Alternatively, the deleted nucleosides may be dispersed throughout the antisense compound, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

[0143] When a single additional subunit is present in a lengthened antisense compound, the additional subunit may be located at the 5' or 3' end of the antisense compound. When two or more additional subunits are present, the added subunits may be adjacent to each other, for example, in an antisense compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the antisense compound. Alternatively, the added subunits may be dispersed throughout the antisense compound, for example, in an antisense compound having one subunit added to the 5' end and one subunit added to the 3' end.

[0144] It is possible to increase or decrease the length of an antisense compound, such as an antisense oligonucleotide, and/or introduce mismatch bases without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of antisense oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Antisense oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the antisense oligonucleotides were able to direct specific cleavage of the target mRNA, albeit to a lesser extent than the antisense oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase antisense oligonucleotides, including those with 1 or 3 mismatches.

[0145] Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bc1-2 mRNA and having 3 mismatches to the bc1-xL mRNA to reduce the expression of both bc1-2 and bc1-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent antitumor activity in vivo.

[0146] Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase antisense oligonucleotides, and a 28 and 42 nucleobase antisense oligonucleotides comprised of the sequence of two or three of the tandem antisense oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase antisense oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase antisense oligonucleotides.

Antisense Compound Motifs

[0147] In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid have chemically modified subunits arranged in patterns, or motifs, to confer to the antisense compounds properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by in vivo nucleases.

[0148] Chimeric antisense compounds typically contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of a chimeric antisense compound may optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

[0149] Antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal region having a plurality of nucleotides that supports RNaseH cleavage is positioned between external regions having a plurality of nucleotides that are chemically distinct from the nucleosides of the internal region. In the case of an antisense oligonucleotide having a gapmer motif, the gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified nucleosides. In certain embodiments, the regions of a gapmer are differentiated by the types of sugar moieties comprising each distinct region. The types of sugar moieties that are used to differentiate the regions of a gapmer may in some embodiments include β-D-ribonucleosides, β-D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides may include 2'-MOE, and 2'-O—CH_3, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides may include those having a 4'-(CH_2)n-O-2' bridge, where n=1 or n=2 and 4'-CH_2—O—CH_2-2'). Preferably, each distinct region comprises uniform sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5' wing region, "Y" represents the length of the gap region, and "Z" represents the length of the 3' wing region. As used herein, a gapmer described as "X-Y-Z" has a configuration such that the gap segment is positioned immediately adjacent to each of the 5' wing segment and the 3' wing segment. Thus, no intervening nucleotides exist between the 5' wing segment and gap segment, or the gap segment and the 3' wing segment. Any of the antisense compounds described herein can have a gapmer motif. In some embodiments, X and Z are the same, in other embodiments they are different. In a preferred embodiment, Y is between 8 and 15 nucleotides. X, Y or Z can be any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or more nucleotides. Thus, gapmers described herein include, but are not limited to, for example 5-10-5, 5-10-4, 4-10-4, 4-10-3, 3-10-3, 2-10-2, 5-9-5, 5-9-4, 4-9-5, 5-8-5, 5-8-4, 4-8-5, 5-7-5, 4-7-5, 5-7-4, or 4-7-4.

[0150] In certain embodiments, the antisense compound has a "wingmer" motif, having a wing-gap or gap-wing configuration, i.e. an X-Y or Y-Z configuration as described above for the gapmer configuration. Thus, wingmer configurations described herein include, but are not limited to, for example 5-10, 8-4, 4-12, 12-4, 3-14, 16-2, 18-1, 10-3, 2-10, 1-10, 8-2, 2-13, 5-13, 5-8, or 6-8.

[0151] In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 5-10-5 gapmer motif. In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 5-10-4 gapmer motif.

[0152] In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 4-10-4 gapmer motif.

[0153] In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 4-10-3 gapmer motif.

[0154] In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid possess a 5-9-5 gapmer motif.

[0155] In certain embodiments, an antisense compound targeted to a C9ORF72 nucleic acid has a gap-narrowed motif. In certain embodiments, a gap-narrowed antisense oligonucleotide targeted to a C9ORF72 nucleic acid has a gap segment of 9, 8, 7, or 6 2'-deoxynucleotides positioned immediately adjacent to and between wing segments of 5, 4, 3, 2, or 1 chemically modified nucleosides. In certain embodiments, the chemical modification comprises a bicyclic sugar. In certain embodiments, the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-$(CH_2)_n$—O-2' bridge, wherein n is 1 or 2; and 4'-CH_2—O—CH_2-2'. In certain embodiments, the bicyclic sugar is comprises a 4'-$CH(CH_3)$—O-2' bridge. In certain embodiments, the chemical modification comprises a non-bicyclic 2'-modified sugar moiety. In certain embodiments, the non-bicyclic 2'-modified sugar moiety comprises a 2'-O-methylethyl group or a 2'-O-methyl group.

[0156] In certain embodiments, an antisense compound targeted to a C9ORF72 nucleic acid is uniformly modified. In certain embodiments, the antisense compound comprises 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleosides. In certain embodiments, each nucleosides is chemically modified. In certain embodiments, the chemical modification comprises a non-bicyclic 2'-modified sugar moiety. In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methoxyethyl group. In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methyl group. In certain embodiments, uniformly modified antisense compounds may target C9ORF72, or any portion thereof, such as a hexanucleotide repeat expansion. In certain embodiments, targeting the hexanucleotide repeat expansion with a unformily modified antisense compound reduces the repeat RNA by blocking the interaction with RNA binding proteins. In certain embodiments, this results in the toxic RNA being absent from foci and being degraded instead.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

[0157] Nucleotide sequences that encode C9ORF72 include, without limitation, the following: the complement of GENBANK Accession No. NM 001256054.1 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT 008413.18 truncated from nucleobase 27535000 to 27565000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No. BQ068108.1 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. NM_018325.3 (incorporated herein as SEQ ID NO: 4), GENBANK Accession No. DN993522.1 (incorporated herein as SEQ ID NO: 5), GENBANK Accession No. NM_145005.5 (incorporated herein as SEQ ID NO: 6), GENBANK Accession No. DB079375.1 (incorporated herein as SEQ ID NO: 7), GENBANK Accession No. BU194591.1 (incorporated herein as SEQ ID NO: 8), Sequence Identifier 4141_014_A (incorporated herein as SEQ ID NO: 9), and Sequence Identifier 4008_73_A (incorporated herein as SEQ ID NO: 10).

[0158] It is understood that the sequence set forth in each SEQ ID NO in the Examples contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

[0159] In certain embodiments, a target region is a structurally defined region of the target nucleic acid. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. The structurally defined regions for C9ORF72 can be obtained by accession number from sequence databases such as NCBI and such information is incorporated herein by reference. In certain embodiments, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the same target region.

[0160] Targeting includes determination of at least one target segment to which an antisense compound hybridizes, such that a desired effect occurs. In certain embodiments, the desired effect is a reduction in mRNA target nucleic acid levels. In certain embodiments, the desired effect is reduction of levels of protein encoded by the target nucleic acid or a phenotypic change associated with the target nucleic acid.

[0161] A target region may contain one or more target segments. Multiple target segments within a target region may be overlapping. Alternatively, they may be non-overlapping. In certain embodiments, target segments within a target region are separated by no more than about 300 nucleotides. In certain embodiments, target segments within a target region are separated by a number of nucleotides that is, is about, is no more than, is no more than about, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10 nucleotides on the target nucleic acid, or is a range defined by any two of the preceeding values. In certain embodiments, target segments within a target region are separated by no more than, or no more than about, 5 nucleotides on the target nucleic acid. In certain embodiments, target segments are contiguous. Contemplated are target regions defined by a range having a starting nucleic acid that is any of the 5' target sites or 3' target sites listed herein.

[0162] Suitable target segments may be found within a 5' UTR, a coding region, a 3' UTR, an intron, an exon, or an exon/intron junction. Target segments containing a start codon or a stop codon are also suitable target segments. A suitable target segment may specifically exclude a certain structurally defined region such as the start codon or stop codon.

[0163] The determination of suitable target segments may include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm may be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that may hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

[0164] There may be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within a target region. In certain

embodiments, reductions in C9ORF72 mRNA levels are indicative of inhibition of C9ORF72 expression. Reductions in levels of a C9ORF72 protein are also indicative of inhibition of target mRNA expression. Reduction in the presence of expanded C9ORF72 RNA foci are indicative of inhibition of C9ORF72 expression. Further, phenotypic changes are indicative of inhibition of C9ORF72 expression. For example, improved motor function and respiration may be indicative of inhibition of C9ORF72 expression.

Hybridization

[0165] In some embodiments, hybridization occurs between an antisense compound disclosed herein and a C9ORF72 nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary nucleobases of the nucleic acid molecules.

[0166] Hybridization can occur under varying conditions. Stringent conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

[0167] Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art. In certain embodiments, the antisense compounds provided herein are specifically hybridizable with a C9ORF72 nucleic acid.

Complementarity

[0168] An antisense compound and a target nucleic acid are complementary to each other when a sufficient number of nucleobases of the antisense compound can hydrogen bond with the corresponding nucleobases of the target nucleic acid, such that a desired effect will occur (e.g., antisense inhibition of a target nucleic acid, such as a C9ORF72 nucleic acid).

[0169] Non-complementary nucleobases between an antisense compound and a C9ORF72 nucleic acid may be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound may hybridize over one or more segments of a C9ORF72 nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

[0170] In certain embodiments, the antisense compounds provided herein, or a specified portion thereof, are, or are at least, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a C9ORF72 nucleic acid, a target region, target segment, or specified portion thereof. Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods.

[0171] For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having 4 (four) noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul et al., J. Mol. Biol., 1990, 215, 403 410; Zhang and Madden, Genome Res., 1997, 7, 649 656). Percent homology, sequence identity or complementarity, can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482 489).

[0172] In certain embodiments, the antisense compounds provided herein, or specified portions thereof, are fully complementary (i.e., 100% complementary) to a target nucleic acid, or specified portion thereof. For example, an antisense compound may be fully complementary to a C9ORF72 nucleic acid, or a target region, or a target segment or target sequence thereof. As used herein, "fully complementary" means each nucleobase of an antisense compound is capable of precise base pairing with the corresponding nucleobases of a target nucleic acid. For example, a 20 nucleobase antisense compound is fully complementary to a target sequence that is 400 nucleobases long, so long as there is a corresponding 20 nucleobase portion of the target nucleic acid that is fully complementary to the antisense compound. Fully complementary can also be used in reference to a specified portion of the first and/or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase antisense compound can be "fully complementary" to a target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase oligonucleotide is fully complementary to the target sequence if the target sequence has a corresponding 20 nucleobase portion wherein each nucleobase is complementary to the 20 nucleobase portion of the antisense compound. At the same time, the entire 30 nucleobase antisense compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the antisense compound are also complementary to the target sequence.

[0173] The location of a non-complementary nucleobase may be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they may be contiguous (i.e., linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer antisense oligonucleotide.

[0174] In certain embodiments, antisense compounds that are, or are up to 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a C9ORF72 nucleic acid, or specified portion thereof.

[0175] In certain embodiments, antisense compounds that are, or are up to 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2, or no more than 1

non-complementary nucleobase(s) relative to a target nucleic acid, such as a C9ORF72 nucleic acid, or specified portion thereof.

[0176] The antisense compounds provided herein also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an antisense compound. In certain embodiments, the antisense compounds, are complementary to at least an 8 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 9 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 10 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least an 11 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 12 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 13 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 14 nucleobase portion of a target segment. In certain embodiments, the antisense compounds, are complementary to at least a 15 nucleobase portion of a target segment. Also contemplated are antisense compounds that are complementary to at least a 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

[0177] The antisense compounds provided herein may also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific Isis number, or portion thereof. As used herein, an antisense compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the antisense compounds described herein as well as compounds having non-identical bases relative to the antisense compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the antisense compound. Percent identity of an antisense compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

[0178] In certain embodiments, the antisense compounds, or portions thereof, are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the antisense compounds or SEQ ID NOs, or a portion thereof, disclosed herein.

[0179] In certain embodiments, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

[0180] In certain embodiments, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Modifications

[0181] A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

[0182] Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

[0183] Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

[0184] The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

[0185] Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

[0186] In certain embodiments, antisense compounds targeted to a C9ORF72 nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

Modified Sugar Moieties

[0187] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substitutent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or $C(R_1)(R_2)$ (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (see PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a BNA (see PCT International Application WO 2007/134181 Published on Nov. 22, 2007 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[0188] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (R or S), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F and 2'-$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2SCH_3$, $O(CH_2)_2$—O—$N(R_m)(R_n)$, O—CH_2—C(═O)—$N(R_m)(R_n)$, and O—CH_2—C(═O)—$N(R_1)$—$(CH_2)_2$—$N(R_m)(R_n)$, where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[0189] As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)—O-2' (LNA); 4'-(CH_2)—S-2; 4'-$(CH_2)_2$—O-2' (ENA); 4'-$CH(CH_3)$—O-2' and 4'-$CH(CH_2OCH_3)$—O-2' (and analogs thereof see U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-$C(CH_3)(CH_3)$—O-2' (and analogs thereof see published International Application WO/2009/006478, published Jan. 8, 2009); 4'-CH_2—$N(OCH_3)$-2' (and analogs thereof see published International Application WO/2008/150729, published Dec. 11, 2008); 4'-CH_2—O—$N(CH_3)$-2' (see published U.S. Patent Application US2004-0171570, published Sep. 2, 2004); 4'-CH_2—N(R)—O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH_2—$C(H)(CH_3)$-2' (see Chattopadhyaya et al., *J. Org. Chem.,* 2009, 74, 118-134); and 4'-CH_2—C—$(═CH_2)$-2' (and analogs thereof see published International Application WO 2008/154401, published on Dec. 8, 2008).

[0190] Further reports related to bicyclic nucleosides can also be found in published literature (see for example: Singh et al., *Chem. Commun.,* 1998, 4, 455-456; Koshkin et al., *Tetrahedron,* 1998, 54, 3607-3630; Wahlestedt et al., *Proc. Natl. Acad. Sci. U.S.A,* 2000, 97, 5633-5638; Kumar et al., *Bioorg. Med. Chem. Lett.,* 1998, 8, 2219-2222; Singh et al., *J. Org. Chem.,* 1998, 63, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.,* 2007, 129(26) 8362-8379; Elayadi et al., *Curr. Opinion Invest. Drugs,* 2001, 2, 558-561; Braasch et al., *Chem. Biol.,* 2001, 8, 1-7; and Orum et al., *Curr. Opinion Mol. Ther.,* 2001, 3, 239-243; U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Ser. Nos. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on Mar. 25, 1999 as WO 99/14226).

[0191] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_a)(R_b)]_n$—, —$C(R_a)$═$C(R_b)$—, —$C(R_a)$═N—, —C(═O)—, —C(═NR_a)—, —C(═S)—, —O—, —$Si(R_a)_2$—, —$S(═O)_x$—, and —$N(R_a)$—;

[0192] wherein:

[0193] x is 0, 1, or 2;

[0194] n is 1, 2, 3, or 4;

[0195] each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(═O)—H), substituted acyl, CN, sulfonyl ($S(═O)_2$-J_1), or sulfoxyl (S(═O)-J_1); and

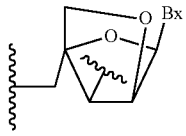
[0196] each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(═O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[0197] In certain embodiments, the bridge of a bicyclic sugar moiety is —$[C(R_a)(R_b)]_n$—, —$[C(R_a)(R_b)]_n$—O—, —$C(R_aR_b)$—N(R)—O— or —$C(R_aR_b)$—O—N(R)—. In certain embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'-CH_2—O—N(R)-2' and 4'-CH_2—N(R)—O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl.

[0198] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2—O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research,* 2003, 21, 6365-6372).

[0199] In certain embodiments, bicyclic nucleosides include, but are not limited to, (A) α-L-methyleneoxy (4'-CH_2—O-2') BNA, (B) β-D-methyleneoxy (4'-CH_2—O-2') BNA, (C) ethyleneoxy (4'-$(CH_2)_2$—O-2') BNA, (D) aminooxy (4'-CH_2—O—N(R)-2') BNA, (E) oxyamino (4'-CH_2—N(R)—O-2') BNA, and (F) methyl(methyleneoxy) (4'-$CH(CH_3)$—O-2') BNA, (G) methylene-thio (4'-CH_2—S-2') BNA, (H) methylene-amino (4'-CH_2—N(R)-2') BNA, (I) methyl carbocyclic (4'-CH_2—$CH(CH_3)$-2') BNA, and (J) propylene carbocyclic (4'-$(CH_2)_3$-2') BNA as depicted below.

(A)



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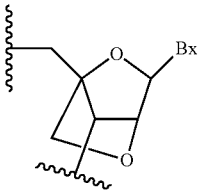

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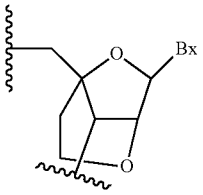

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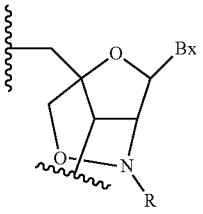

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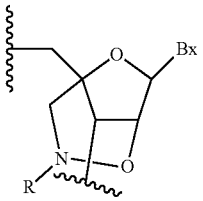

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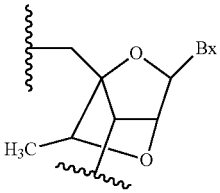

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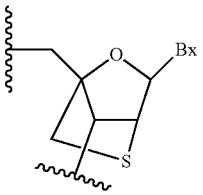
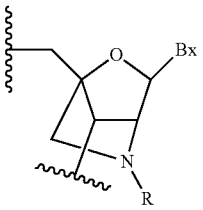
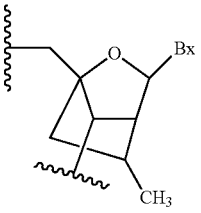
(G)



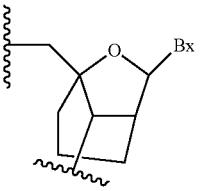
(H)



(I)



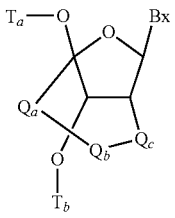
(J)



wherein Bx is the base moiety and R is independently H, a protecting group or C_1-C_{12} alkyl.

[0200] In certain embodiments, bicyclic nucleosides are provided having Formula I:

I



wherein:

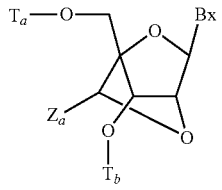
[0201] Bx is a heterocyclic base moiety;

[0202] $-Q_a-Q_b-Q_c-$ is $—CH_2—N(R_c)—CH_2—$, $—C(=O)—N(R_c)—CH_2—$, $—CH_2—O—N(R_c)—$, $—CH_2—N(R_c)—O—$ or $—N(R_c)—O—CH_2$;

[0203] R_c is C_1-C_{12} alkyl or an amino protecting group; and

[0204] T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium.

[0205] In certain embodiments, bicyclic nucleosides are provided having Formula II:



II

wherein:

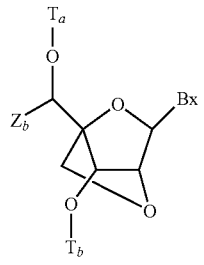
[0206] Bx is a heterocyclic base moiety;

[0207] T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

[0208] Z_a is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, substituted amide, thiol or substituted thio.

[0209] In one embodiment, each of the substituted groups is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ_c, NJ_cJ_d, SJ_c, N_3, $OC(=X)J_c$, and $NJ_eC(=X)NJ_cJ_d$, wherein each J_c, J_d and J_e is, independently, H, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl and X is O or NJ_c.

[0210] In certain embodiments, bicyclic nucleosides are provided having Formula III:



III

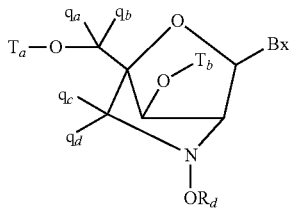
wherein:

[0211] Bx is a heterocyclic base moiety;

[0212] T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

[0213] Z_b is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl or substituted acyl (C(=O)—).

[0214] In certain embodiments, bicyclic nucleosides are provided having Formula IV:



IV

wherein:

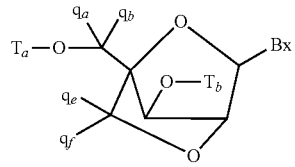
[0215] Bx is a heterocyclic base moiety;

[0216] T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

[0217] R_d is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

[0218] each q_a, q_b, q_c and q_d is, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl, C_1-C_6 alkoxyl, substituted C_1-C_6 alkoxyl, acyl, substituted acyl, C_1-C_6 aminoalkyl or substituted C_1-C_6 aminoalkyl;

[0219] In certain embodiments, bicyclic nucleosides are provided having Formula V:



V

wherein:

[0220] Bx is a heterocyclic base moiety;

[0221] T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

[0222] q_a, q_b, q_e and q_f are each, independently, hydrogen, halogen, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, substituted C_1-C_{12} alkoxy, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O—C(=O)NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)NJ_jJ_k$ or $N(H)C(=S)NJ_jJ_k$;

[0223] or q_e and q_f together are $=C(q_g)(q_h)$;

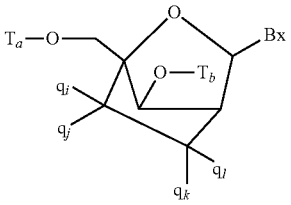
[0224] q_g and q_h are each, independently, H, halogen, C_1-C_{12} alkyl or substituted C_1-C_{12} alkyl.

[0225] The synthesis and preparation of the methyleneoxy (4'-CH_2—O-2') BNA monomers adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin et al., *Tetrahedron,* 1998, 54, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

[0226] Analogs of methyleneoxy (4'-CH_2—O-2') BNA and 2'-thio-BNAs, have also been prepared (Kumar et al., *Bioorg. Med. Chem. Lett.,* 1998, 8, 2219-2222). Preparation of locked nucleoside analogs comprising oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel et al., WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel comformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh et al., *J. Org. Chem.,* 1998, 63, 10035-10039). In addition, 2'-amino- and 2'-methylamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

[0227] In certain embodiments, bicyclic nucleosides are provided having Formula VI:

VI



wherein:

[0228] Bx is a heterocyclic base moiety;

[0229] T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

[0230] each q_i, q_j, q_k and q_l is, independently, H, halogen, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_1-C_{12} alkoxyl, substituted C_1-C_{12} alkoxyl, OJ_T, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O—C(=O)NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)NJ_jJ_k$ or $N(H)C(=S)NJ_jJ_k$; and

[0231] q_i and q_j or q_l and q_k together are $=C(q_g)(q_h)$, wherein q_g and q_h are each, independently, H, halogen, C_1-C_{12} alkyl or substituted C_1-C_{12} alkyl.

[0232] One carbocyclic bicyclic nucleoside having a 4'-$(CH_2)_3$-2' bridge and the alkenyl analog bridge 4'-CH=CH—CH_2-**2'** have been described (Freier et al., *Nucleic Acids Research,* 1997, 25(22), 4429-4443 and Albaek et al., *J. Org. Chem.,* 2006, 71, 7731-7740). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (Srivastava et al., *J. Am. Chem. Soc.,* 2007, 129(26), 8362-8379).

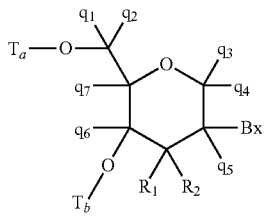
[0233] As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2' carbon atom and the 4' carbon atom of the sugar ring.

[0234] As used herein, "monocylic nucleosides" refer to nucleosides comprising modified sugar moieties that are not bicyclic sugar moieties. In certain embodiments, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position.

[0235] As used herein, "2'-modified sugar" means a furanosyl sugar modified at the 2' position. In certain embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In certain embodiments, 2' modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nF$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other 2'-substituent groups can also be selected from: C_1-C_{12} alkyl, substituted alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, F, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving pharmacokinetic properties, or a group for improving the pharmacodynamic properties of an antisense compound, and other substituents having similar properties. In certain embodiments, modified nucleosides comprise a 2'-MOE side chain (Baker et al., *J. Biol. Chem.,* 1997, 272, 11944-12000). Such 2'-MOE substitution have been described as having improved binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2'-O-methyl, O-propyl, and O-aminopropyl. Oligonucleotides having the 2'-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for in vivo use (Martin, *Helv. Chim. Acta,* 1995, 78, 486-504; Altmann et al., *Chimia,* 1996, 50, 168-176; Altmann et al., *Biochem. Soc. Trans.,* 1996, 24, 630-637; and Altmann et al., *Nucleosides Nucleotides,* 1997, 16, 917-926).

[0236] As used herein, a "modified tetrahydropyran nucleoside" or "modified THP nucleoside" means a nucleoside having a six-membered tetrahydropyran "sugar" substituted in for the pentofuranosyl residue in normal nucleosides (a sugar surrogate). Modified THP nucleosides include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see Leumann, *Bioorg. Med. Chem.,* 2002, 10, 841-854), fluoro HNA (F-HNA) or those compounds having Formula VII:

VII



wherein independently for each of said at least one tetrahydropyran nucleoside analog of Formula VII:

[0237] Bx is a heterocyclic base moiety;

[0238] T_a and T_b are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_a and T_b is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_a and T_b is H, a hydroxyl protecting group, a linked conjugate group or a 5' or 3'-terminal group;

[0239] q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl,

substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl; and each of R_1 and R_2 is selected from hydrogen, hydroxyl, halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ and CN, wherein X is O, S or NJ_1 and each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl.

[0240] In certain embodiments, the modified THP nucleosides of Formula VII are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, THP nucleosides of Formula VII are provided wherein one of R_1 and R_2 is fluoro. In certain embodiments, R_1 is fluoro and R_2 is H; R_1 is methoxy and R_2 is H, and R_1 is H and R_2 is methoxyethoxy.

[0241] As used herein, "2'-modified" or "2'-substituted" refers to a nucleoside comprising a sugar comprising a substituent at the 2' position other than H or OH. 2'-modified nucleosides, include, but are not limited to, bicyclic nucleosides wherein the bridge connecting two carbon atoms of the sugar ring connects the 2' carbon and another carbon of the sugar ring; and nucleosides with non-bridging 2' substituents, such as allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, —OCF_3, O—$(CH_2)_2$—O—CH_3, 2'-$O(CH_2)_2SCH_3$, O—$(CH_2)_2$—O—$N(R_m)(R_n)$, or O—CH_2—C(=O)—$N(R_m)(R_n)$, where each R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. 2'-modified nucleosides may further comprise other modifications, for example at other positions of the sugar and/or at the nucleobase.

[0242] As used herein, "2'-F" refers to a nucleoside comprising a sugar comprising a fluoro group at the 2' position.

[0243] As used herein, "2'-OMe" or "2'-OCH_3" or "2'-O-methyl" each refers to a nucleoside comprising a sugar comprising an —OCH_3 group at the 2' position of the sugar ring.

[0244] As used herein, "MOE" or "2'-MOE" or "2'-$OCH_2CH_2OCH_3$" or "2'-O-methoxyethyl" each refers to a nucleoside comprising a sugar comprising a —$OCH_2CH_2OCH_3$ group at the 2' position of the sugar ring.

[0245] As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain embodiments, one or more of the plurality of nucleosides is modified. In certain embodiments, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA).

[0246] Many other bicyclo and tricyclo sugar surrogate ring systems are also known in the art that can be used to modify nucleosides for incorporation into antisense compounds (see for example review article: Leumann, *Bioorg. Med. Chem.,* 2002, 10, 841-854).

Such ring systems can undergo various additional substitutions to enhance activity.

[0247] Methods for the preparations of modified sugars are well known to those skilled in the art.

[0248] In nucleotides having modified sugar moieties, the nucleobase moieties (natural, modified or a combination thereof) are maintained for hybridization with an appropriate nucleic acid target.

[0249] In certain embodiments, antisense compounds comprise one or more nucleosides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE. In certain embodiments, the 2'-MOE modified nucleosides are arranged in a gapmer motif. In certain embodiments, the modified sugar moiety is a bicyclic nucleoside having a (4'-$CH(CH_3)$—O-2') bridging group. In certain embodiments, the (4'-$CH(CH_3)$—O-2') modified nucleosides are arranged throughout the wings of a gapmer motif.

Compositions and Methods for Formulating Pharmaceutical Compositions

[0250] Antisense oligonucleotides may be admixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

[0251] An antisense compound targeted to a C9ORF72 nucleic acid can be utilized in pharmaceutical compositions by combining the antisense compound with a suitable pharmaceutically acceptable diluent or carrier. A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS). PBS is a diluent suitable for use in compositions to be delivered parenterally. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising an antisense compound targeted to a C9ORF72 nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is PBS. In certain embodiments, the antisense compound is an antisense oligonucleotide.

[0252] Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of antisense compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

[0253] A prodrug can include the incorporation of additional nucleosides at one or both ends of an antisense compound which are cleaved by endogenous nucleases within the body, to form the active antisense compound.

Conjugated Antisense Compounds

[0254] Antisense compounds may be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the resulting antisense oligonucleotides. Typical conjugate groups include cholesterol moieties and lipid moieties. Additional conjugate groups include carbohydrates, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

[0255] Antisense compounds can also be modified to have one or more stabilizing groups that are generally attached to one or both termini of antisense compounds to enhance properties such as, for example, nuclease stability. Included in stabilizing groups are cap structures. These terminal modifications protect the antisense compound having terminal nucleic acid from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap), or at the 3'-terminus

(3'-cap), or can be present on both termini. Cap structures are well known in the art and include, for example, inverted deoxy abasic caps. Further 3' and 5'-stabilizing groups that can be used to cap one or both ends of an antisense compound to impart nuclease stability include those disclosed in WO 03/004602 published on Jan. 16, 2003.

Cell Culture and Antisense Compounds Treatment

[0256] The effects of antisense compounds on the level, activity or expression of C9ORF72 nucleic acids can be tested in vitro in a variety of cell types. Cell types used for such analyses are available from commercial vendors (e.g. American Type Culture Collection, Manassas, Va.; Zen-Bio, Inc., Research Triangle Park, N.C.; Clonetics Corporation, Walkersville, Md.) and are cultured according to the vendor's instructions using commercially available reagents (e.g. Invitrogen Life Technologies, Carlsbad, Calif.). Illustrative cell types include, but are not limited to, HepG2 cells, Hep3B cells, and primary hepatocytes.

In Vitro Testing of Antisense Oligonucleotides

[0257] Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

[0258] In general, cells are treated with antisense oligonucleotides when the cells reach approximately 60-80% confluency in culture.

[0259] One reagent commonly used to introduce antisense oligonucleotides into cultured cells includes the cationic lipid transfection reagent LIPOFECTIN (Invitrogen, Carlsbad, Calif.). Antisense oligonucleotides are mixed with LIPOFECTIN in OPTI-MEM 1 (Invitrogen, Carlsbad, Calif.) to achieve the desired final concentration of antisense oligonucleotide and a LIPOFECTIN concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

[0260] Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE (Invitrogen, Carlsbad, Calif.). Antisense oligonucleotide is mixed with LIPOFECTAMINE in OPTI-MEM 1 reduced serum medium (Invitrogen, Carlsbad, Calif.) to achieve the desired concentration of antisense oligonucleotide and a LIPOFECTAMINE concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

[0261] Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation.

[0262] Cells are treated with antisense oligonucleotides by routine methods. Cells are typically harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein. In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

[0263] The concentration of anti sense oligonucleotide used varies from cell line to cell line. Methods to determine the optimal antisense oligonucleotide concentration for a particular cell line are well known in the art. Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM when transfected with LIPOFECTAMINE. Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using electroporation.

RNA Isolation

[0264] RNA analysis can be performed on total cellular RNA or poly(A)+mRNA. Methods of RNA isolation are well known in the art. RNA is prepared using methods well known in the art, for example, using the TRIZOL Reagent (Invitrogen, Carlsbad, Calif.) according to the manufacturer's recommended protocols.

Analysis of Inhibition of Target Levels or Expression

[0265] Inhibition of levels or expression of a C9ORF72 nucleic acid can be assayed in a variety of ways known in the art. For example, target nucleic acid levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitaive real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+mRNA. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Quantitative real-time PCR can be conveniently accomplished using the commercially available ABI PRISM 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, Calif. and used according to manufacturer's instructions.

Quantitative Real-Time PCR Analysis of Target RNA Levels

[0266] Quantitation of target RNA levels may be accomplished by quantitative real-time PCR using the ABI PRISM 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, Calif.) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

[0267] Prior to real-time PCR, the isolated RNA is subjected to a reverse transcriptase (RT) reaction, which produces complementary DNA (cDNA) that is then used as the substrate for the real-time PCR amplification. The RT and real-time PCR reactions are performed sequentially in the same sample well. RT and real-time PCR reagents are obtained from Invitrogen (Carlsbad, Calif.). RT real-time-PCR reactions are carried out by methods well known to those skilled in the art.

[0268] Gene (or RNA) target quantities obtained by real time PCR are normalized using either the expression level of a gene whose expression is constant, such as cyclophilin A, or by quantifying total RNA using RIBOGREEN (Invitrogen, Inc. Carlsbad, Calif.). Cyclophilin A expression is quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RIBOGREEN RNA quantification reagent (Invetrogen, Inc. Eugene, Oreg.). Methods of RNA quantification by RIBOGREEN are taught in Jones, L. J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR 4000 instrument (PE Applied Biosystems) is used to measure RIBOGREEN fluorescence.

[0269] Probes and primers are designed to hybridize to a C9ORF72 nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS Software (Applied Biosystems, Foster City, Calif.).

Analysis of Protein Levels

[0270] Antisense inhibition of C9ORF72 nucleic acids can be assessed by measuring C9ORF72 protein levels. Protein levels of C9ORF72 can be evaluated or quantitated in a

variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA), quantitative protein assays, protein activity assays (for example, caspase activity assays), immunohistochemistry, immunocytochemistry or fluorescence-activated cell sorting (FACS). Antibodies directed to a target can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, Mich.), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art. Antibodies useful for the detection of mouse, rat, monkey, and human C9ORF72 are commercially available.

In Vivo Testing of Antisense Compounds

[0271] Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of C9ORF72 and produce phenotypic changes, such as, improved motor function and respiration. In certain embodiments, motor function is measured by rotarod, grip strength, pole climb, open field performance, balance beam, hindpaw footprint testing in the animal. In certain embodiments, respiration is measured by whole body plethysmograph, invasive resistance, and compliance measurements in the animal. Testing may be performed in normal animals, or in experimental disease models. For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as phosphate-buffered saline. Administration includes parenteral routes of administration, such as intraperitoneal, intravenous, and subcutaneous. Calculation of antisense oligonucleotide dosage and dosing frequency is within the abilities of those skilled in the art, and depends upon factors such as route of administration and animal body weight. Following a period of treatment with antisense oligonucleotides, RNA is isolated from CNS tissue or CSF and changes in C9ORF72 nucleic acid expression are measured.

Targeting C9ORF72

[0272] Antisense oligonucleotides described herein may hybridize to a C9ORF72 nucleic acid in any stage of RNA processing. For example, described herein are antisense oligonucleotides that are complementary to a pre-mRNA or a mature mRNA. Additionally, antisense oligonucleotides described herein may hybridize to any element of a C9ORF72 nucleic acid. For example, described herein are antisense oligonucleotides that are complementary to an exon, an intron, the 5' UTR, the 3' UTR, a repeat region, a hexanucleotide repeat expansion, a splice junction, an exon: exon splice junction, an exonic splicing silencer (ESS), an exonic splicing enhancer (ESE), exon 1a, exon 1b, exon 1c, exon 1d, exon 1e, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, intron 1, intron 2, intron 3, intron 4, intron 5, intron 6, intron 7, intron 8, intron 9, or intron 10 of a C9ORF72 nucleic acid.

[0273] In certain embodiments, antisense oligonucleotides described herein hybridize to all variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein selectively hybridize to certain variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein selectively hybridize to variants of C9ORF72 containing a hexanucleotide repeat expansion. In certain embodiments, such variants of C9ORF72 containing a hexanucleotide repeat expansion include SEQ ID NO: 1-3 and 6-10. In certain embodiments, such hexanucleotide repeat expansion comprises at least 30 repeats of any of GGGGCC, GGGGGG, GGGGGC, or GGGGCG.

[0274] In certain embodiments, the antisense oligonucleotides described herein inhibit expression of all variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein inhibit expression of all variants of C9ORF72 equally. In certain embodiments, the antisense oligonucleotides described herein preferentially inhibit expression of certain variants of C9ORF72. In certain embodiments, the antisense oligonucleotides described herein preferentially inhibit expression of variants of C9ORF72 containing a hexanucleotide repeat expansion. In certain embodiments, such variants of C9ORF72 containing a hexanucleotide repeat expansion include SEQ ID NO: 1-3 and 6-10. In certain embodiments, such hexanucleotide repeat expansion comprises at least 30 repeats of any of GGGGCC, GGGGGG, GGGGGC, or GGGGCG. In certain embodiments, the hexanucleotide repeat expansion forms nuclear foci. In certain embodiments, antisense oligonucleotides described herein are useful for reducing nuclear foci. Nuclear foci may be reduced in terms of percent of cells with foci as well as number of foci per cell.

[0275] Based on earlier studies directed to repeat expansions, it is not possible to predict if antisense oligonucleotides targeting C9ORF72 outside of the hexanucleotide repeat expansion would successfully inhibit expression of C9ORF72 for two reasons. First, the C9ORF72 repeat expansion is located in an intron and it is not known if the RNA in the foci contains only the repeats or also the flanking intronic sequence. For example, an earlier study on myotonic dystrophy type 2 (DM2), which is a disease caused by a CCTG expansion mutation in intron 1 of the ZNF9 gene, determined that large DM2 expansions did not prevent allele-specific pre-mRNA splicing, nuclear export of the transcripts, or steady-state mRNA or protein levels. The study further demonstrated that the ribonuclear inclusions found associated with the disease are enriched for the CCUG expansion, but not the flanking intronic sequences. These data suggest that the downstream molecular effects of the DM2 mutation may be triggered by the accumulation of CCUG repeat tract alone. Therefore, this study implies that targeting the CCUG repeat expansion alone would lead to amelioration of the disease, since targeting the flanking sequences, especially the region downstream of the repeat expansion, would not affect the formation of ribonuclear inclusions (Margolis et al. Hum. Mol. Genet., 2006, 15:1808-1815). Second, it is not known how fast intron 1 of C9ORF72, which contains the repeats, is excised and accumulates in foci. Thus, it is not possible to predict if targeting the pre-mRNA would result in elimination of the repeat RNA and foci.

C9OFF72 Features

[0276] Antisense oligonucleotides described herein may hybridize to any C9ORF72 variant at any state of processing within any element of the C9ORF72 gene. For example, antisense oligonucleotides described herein may hybridize to an exon, an intron, the 5' UTR, the 3' UTR, a repeat region, a hexanucleotide repeat expansion, a splice junction, an exon:exon splice junction, an exonic splicing silencer (ESS), an exonic splicing enhancer (ESE), exon 1a, exon 1b, exon 1c, exon 1d, exon 1e, exon 2, exon 3, exon 4, exon 5,

exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, intron 1, intron 2, intron 3, intron 4, intron 5, intron 6, intron 7, intron 8, intron 9, or intron 10. For example, antisense oligonucleotides may target any of the exons characterized below in Tables 1-5 for the various C9ORF72 variants described below. Antisense oligonucleotides described herein may also target variants not characterized below and such variants are characterized in GENBANK. Moreover, antisense oligonucleotides described herein may also target elements other than exons and such elements are characterized in GENBANK.

TABLE 1

Functional Segments for NM_001256054.1 (SEQ ID NO: 1)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1C	1	158	1137	1294
exon 2	159	646	7839	8326
exon 3	647	706	9413	9472
exon 4	707	802	12527	12622
exon 5	803	867	13354	13418
exon 6	868	940	14704	14776
exon 7	941	1057	16396	16512
exon 8	1058	1293	18207	18442
exon 9	1294	1351	24296	24353
exon 10	1352	1461	26337	26446
exon 11	1462	3339	26581	28458

TABLE 2

Functional Segments for NM_018325.3 (SEQ ID NO: 4)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1B	1	63	1510	1572
exon 2	64	551	7839	8326
exon 3	552	611	9413	9472
exon 4	612	707	12527	12622
exon 5	708	772	13354	13418
exon 6	773	845	14704	14776
exon 7	846	962	16396	16512
exon 8	963	1198	18207	18442
exon 9	1199	1256	24296	24353
exon 10	1257	1366	26337	26446
exon 11	1367	3244	26581	28458

TABLE 3

Functional Segments for NM_145005.5 (SEQ ID NO: 6)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1A	1	80	1137	1216
exon 2	81	568	7839	8326
exon 3	569	628	9413	9472
exon 4	629	724	12527	12622
exon 5B (exon 5 into intron 5)	725	1871	13354	14500

TABLE 4

Functional Segments for DB079375.1 (SEQ ID NO: 7)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1E	1	35	1135	1169
exon 2	36	524	7839	8326
exon 3 (EST ends before end of full exon)	525	562	9413	9450

TABLE 5

Functional Segments for BU194591.1 (SEQ ID NO: 8)

Exon Number	mRNA start site	mRNA stop site	Start site in reference to SEQ ID NO: 2	Stop site in reference to SEQ ID NO: 2
exon 1D	1	36	1241	1279
exon 2	37	524	7839	8326
exon 3	525	584	9413	9472
exon 4	585	680	12527	12622
exon 5B (exon 5 into intron 5)	681	798	13354	13465

Certain Indications

[0277] In certain embodiments, provided herein are methods of treating an individual comprising administering one or more pharmaceutical compositions described herein. In certain embodiments, the individual has a neurodegenerative disease. In certain embodiments, the individual is at risk for developing a neurodegenerative disease, including, but not limited to, ALS or FTD. In certain embodiments, the individual has been identified as having a C9ORF72 associated disease. In certain embodiments, the individual has been identified as having a C9ORF72 hexanucleotide repeat expansion associated disease. In certain embodiments, provided herein are methods for prophylactically reducing C9ORF72 expression in an individual. Certain embodiments include treating an individual in need thereof by administering to an individual a therapeutically effective amount of an antisense compound targeted to a C9ORF72 nucleic acid.

[0278] In one embodiment, administration of a therapeutically effective amount of an antisense compound targeted to a C9ORF72 nucleic acid is accompanied by monitoring of C9ORF72 levels in an individual, to determine an individual's response to administration of the antisense compound. An individual's response to administration of the antisense compound may be used by a physician to determine the amount and duration of therapeutic intervention.

[0279] In certain embodiments, administration of an antisense compound targeted to a C9ORF72 nucleic acid results in reduction of C9ORF72 expression by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In certain embodiments, administration of an antisense compound targeted to a C9ORF72 nucleic acid results in improved motor function and respiration in an animal. In certain embodiments, administration of a C9ORF72 antisense com-

pound improves motor function and respiration by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0280] In certain embodiments, pharmaceutical compositions comprising an antisense compound targeted to C9ORF72 are used for the preparation of a medicament for treating a patient suffering or susceptible to a neurodegenerative disease including ALS and FTD.

Certain Combination Therapies

[0281] In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease, disorder, or condition as the one or more pharmaceutical compositions described herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease, disorder, or condition as the one or more pharmaceutical compositions described herein. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired side effect of one or more pharmaceutical compositions described herein. In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with another pharmaceutical agent to produce a combinational effect. In certain embodiments, one or more pharmaceutical compositions described herein are co-administered with another pharmaceutical agent to produce a synergistic effect.

[0282] In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical compositions described herein and one or more other pharmaceutical agents are prepared separately.

[0283] In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition described herein include Riluzole (Rilutek), Lioresal (Lioresal), and Dexpramipexole.

[0284] In certain embodiments, pharmaceutical agents that may be co-administered with a C9ORF72 specific inhibitor described herein include, but are not limited to, an additional C9ORF72 inhibitor. In certain embodiments, the co-adminstered pharmaceutical agent is administered prior to administration of a pharmaceutical composition described herein. In certain embodiments, the co-administered pharmaceutical agent is administered following administration of a pharmaceutical composition described herein. In certain embodiments the co-administered pharmaceutical agent is administered at the same time as a pharmaceutical composition described herein. In certain embodiments the dose of a co-administered pharmaceutical agent is the same as the dose that would be administered if the co-administered pharmaceutical agent was administered alone. In certain embodiments the dose of a co-administered pharmaceutical agent is lower than the dose that would be administered if the co-administered pharmaceutical agent was administered alone. In certain embodiments the dose of a co-administered pharmaceutical agent is greater than the dose that would be administered if the co-administered pharmaceutical agent was administered alone.

[0285] In certain embodiments, the co-administration of a second compound enhances the effect of a first compound, such that co-administration of the compounds results in an effect that is greater than the effect of administering the first compound alone. In other embodiments, the co-administration results in effects that are additive of the effects of the compounds when administered alone. In certain embodiments, the co-administration results in effects that are supra-additive of the effects of the compounds when administered alone. In certain embodiments, the first compound is an antisense compound. In certain embodiments, the second compound is an antisense compound.

EXAMPLES

Non-Limiting Disclosure and Incorporation by Reference

[0286] While certain compounds, compositions, and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references recited in the present application is incorporated herein by reference in its entirety.

Example 1: Antisense Inhibition of Human C9ORF72 in HepG2 Cells

[0287] Antisense oligonucleotides were designed targeting a C9ORF72 nucleic acid and were tested for their effects on C9ORF72 mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using electroporation with 7,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3750 (forward sequence TGTGACAGTTGGAATGCAGTGA, designated herein as SEQ ID NO: 15; reverse sequence GCCACTTAAAGCAATCTCTGTCTTG, designated herein as SEQ ID NO: 16; probe sequence TCGACTCTTTGCCCACCGCCA, designated herein as SEQ ID NO: 17) was used to measure mRNA levels. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells.

[0288] The antisense oligonucleotides in Tables 6-10 were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate linkages. All cytosine residues

throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted human gene sequence. Each antisense oligonucleotide listed in Tables 6-9 is targeted to the either human C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_001256054.1) or the human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from nucleosides 27535000 to 27565000), or both. 'n/a' indicates that the antisense oligonucleotide did not target that particular gene sequence. The antisense oligonucleotides of Table 10 are targeted to either SEQ ID NO: 3 (GENBANK Accession No. BQ068108.1) or SEQ ID NO: 4 (GENBANK Accession No. NM_018325.3).

[0289] As shown in Tables 6-10, below, several of the oligonucleotides targeting SEQ ID NO: 1 exhibit at least 50% inhibition, including those targeted to nucleobases 90-647, 728-1541, 1598-1863, 1935-2146, 2232-2251, 2429-2576, 2632-2743, 2788-2807, 2860-2879, 2949-2968, 3062-3081, 3132-3151, and 3250-3269 of SEQ ID NO 1. These include SEQ ID NOs: 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43, 44, 45, 46, 47, 50, 51, 53, 55, 56, 57, 61, 62, 64, 66, 67, 72, 73, 75, 76, 81, 82, 85, 89, 90, 91, 92, 93, 94, 96, 97, 100, 102, 103, 109, 111, 112, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 130, 131, 132, 133, 137, 139, 140, 141, 145, 146, 149, 150, 151, 152, 153, 154, 165, 166, 168, 169, 170, 171, 174, 179, 181, 182, 183, 185, 186, 187, 188, 190, 192, 195, 197, 199, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, and 332. Several of the oligonucleotides exhibit at least 70% inhibition, including those targeted to nucleobases 90-359, 430-479, 550-569, 617-647, 940-959, 1013-1033, 1446-1465, 1687-1706, 1844-1863, 1935-2007, and 2679-2698 of SEQ ID NO 1. These include SEQ ID NOs: 32, 33, 34, 35, 36, 40, 41, 42, 43, 44, 47, 66, 67, 85, 96, 103, 117, 119, 154, 165, 168, 186, 320, 321, 324, 327, 328, and 331. Several of the oligonucleotides exhibit at least 80% inhibition, including those targeted to nucleobases 90-265 and 310-329. These include SEQ ID NOs: 32, 33, 35, 40, 42, and 321. Several of the oligonucleotides exhibit at least 90% inhibition, including those targeted to nucleobases 190-209 and 310-329 of SEQ ID NO 1. These include SEQ ID NOs: 40 and 321.

[0290] As shown in Tables 6-20, below, several of the oligonucleotides targeting SEQ ID NO: 2 exhibit at least 50% inhibition, including those targeted to nucleobases 1552-1572, 2187-2238, 2728-2779, 3452-2471, 3752-3771, 5025-5044, 5656-5675, 6200-6219, 7594-7613, 7840-8328, 9415-9434, 12526-12545, 13357-13524, 13642-13661, 13790-14130, 14243-14335, 14699-14777, 15587-15606, 16395-16488, 18233-18373, 24306-24340, 24472-24491, 24565-24676, 26400-26424, 26606-26982, 27054-27265, 27351-27370, 27548-27998, 28068-28087, 28181-28270, and 28369-28388 of SEQ ID NO 2. These include SEQ ID NOs: 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43, 44, 45, 46, 47, 50, 51, 53, 55, 56, 57, 64, 67, 72, 73, 75, 76, 81, 82, 85, 89, 90, 91, 92, 93, 94, 96, 97, 100, 102, 103, 111, 112, 115, 117, 118, 119, 121, 122, 123, 124, 125, 126, 130, 131, 132, 133, 137, 139, 140, 141, 145, 146, 149, 150, 151, 152, 153, 154, 165, 166, 168, 169, 170, 171, 174, 179, 181, 182, 183, 185, 186, 187, 188, 190, 192, 195, 197, 199, 205, 206, 208, 211, 212, 224, 226, 230, 231, 250, 251, 252, 256, 300, 301, 304, 306, 307, 310, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, and 332. Several of the oligonucleotides exhibit at least 70% inhibition, including those targeted to nucleobases 3452-2471, 7840-8159, 8230-8249, 12526-12545, 13642-13661, 14075-14094, 14316-14335, 14758-14777, 16395-16414, 16469, 16488, 24655-24674, 26963, 26982, 27054-27126, and 27798-27817 of SEQ ID NO 2. These include SEQ ID NOs: 32, 33, 34, 35, 36, 40, 41, 42, 43, 44, 47, 67, 85, 96, 103, 117, 119, 154, 165, 168, 186, 251, 306, 320, 321, 324, 327, 328, and 331. Several of the oligonucleotides exhibit at least 80% inhibition, including those targeted to nucleobases 7848-8023 of SEQ ID NO 2. These include SEQ ID NOs: 32, 33, 35, 40, 42, and 321. Several of the oligonucleotides exhibit at least 90% inhibition, including those targeted to nucleobases 7870-7889 and 7990-8009 of SEQ ID NO 2. These include SEQ ID NOs: 40 and 321.

TABLE 6

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
3	1139	AGCGGGACACCGTAGGTTAC	576883	0	30
44	1180	GTGGGCGGAACTTGTCGCTG	576807	1	31
90	7848	GTCACATTATCCAAATGCTC	576808	85	32
125	7883	GGTGGGCAAAGAGTCGACAT	576809	82	33
155	7913	ATCTCTGTCTTGGCAACAGC	576810	78	34
160	7918	AAGCAATCTCTGTCTTGGCA	576811	81	35
165	7923	ACTTAAAGCAATCTCTGTCT	576812	78	36
170	7928	TTGCCACTTAAAGCAATCTC	576813	67	37
205	7963	CCCAGTAAGCAAAAGTAGCT	576814	66	38
227	7985	ACTCTAGGACCAAGAATATT	576815	11	39

TABLE 6-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
232	7990	GCCTTACTCTAGGACCAAGA	576816	78	40
240	7998	CCAAATGTGCCTTACTCTAG	576817	73	41
246	8004	TGGAGCCCAAATGTGCCTTA	576818	81	42
254	8012	TCTGTCTTTGGAGCCCAAAT	576819	76	43
275	8033	CCATCACTGAGAAGTACCTG	576820	79	44
281	8039	ATTTCTCCATCACTGAGAAG	576821	61	45
288	8046	AAAAGTTATTTCTCCATCAC	576822	57	46
295	8053	TGGCAAGAAAAGTTATTTCT	576823	70	47
302	8060	GTGTGGTTGGCAAGAAAAGT	576824	44	48
313	8071	CTCCATTTAGAGTGTGGTTG	576825	39	49
330	8088	TGCATTTCGAAGGATTTCTC	576826	65	50
338	8096	CCACTCTCTGCATTTCGAAG	576827	67	51
362	8120	ACAAAAAACTTTACATCTAT	576828	22	52
376	8134	CCTTTTCAGACAAGACAAAA	576829	53	53
401	8159	AAGATTAATGAAACAATAAT	576830	0	54
411	8169	GTTTCCATCAAAGATTAATG	576831	62	55
446	8204	ATTGATAGTCCATATGTGCT	576832	59	56
452	8210	AGTATAATTGATAGTCCATA	571818	57	57
481	8239	GGAGGTAGAAACTAAGTTCT	576833	45	58
516	8274	ATGTGTTAATCTATCAACAC	576834	48	59
545	8303	TGCATCCATATTCTTCCTTT	576835	43	60
552	n/a	TTCCTTATGCATCCATATTC	576836	64	61
559	n/a	CTTGTCTTTCCTTATGCATC	576837	57	62
566	n/a	ACATTTTCTTGTCTTTCCTT	576838	43	63
571	9415	TCTGGACATTTTCTTGTCTT	576839	61	64
578	9422	ATAATCTTCTGGACATTTTC	576840	37	65
617	n/a	CTCTGACCCTGATCTTCCAT	576841	79	66
628	12526	TTGGAATAATACTCTGACCC	576842	73	67
663	12561	CAGTTCCATTACAGGAATCA	576843	45	68
697	12595	CTTCAGGAACACTGTGTGAT	576844	20	69
705	12603	ATCTATTTCTTCAGGAACAC	576845	46	70
722	n/a	AGTACTGTATCAGCTATATC	576846	46	71
728	13357	TCATTGAGTACTGTATCAGC	576847	52	72
734	13363	TCATCATCATTGAGTACTGT	576848	67	73
740	13369	CCAATATCATCATCATTGAG	576849	47	74

TABLE 6-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
755	13384	TCATGACAGCTGTCACCAAT	576850	51	75
761	13390	AAGCCTTCATGACAGCTGTC	576851	52	76
767	13396	AGAAGAAAGCCTTCATGACA	576852	23	77
773	13402	TACTTGAGAAGAAAGCCTTC	576853	24	78
778	13407	ATTCTTACTTGAGAAGAAAG	576854	12	79
782	13411	AAAAATTCTTACTTGAGAAG	576855	0	80
817	13446	AGATGGTATCTGCTTCATCC	576856	61	81
876	13505	CAATCTAAGTAGACAGTCTG	576857	57	82
911	13540	TTAAGCAACAGTTCAAATAC	576858	40	83
978	13607	CTTTAAATAGCAAATGGAAT	576859	26	84
1013	13642	GCCATGATTTCTTGTCTGGG	576860	79	85
1056	13685	GCTTTAATGAGAAGTAAAAC	576861	17	86
1091	13720	TCTACAGTACAACTTAATAT	576862	39	87
1126	13755	ATAATTTTGTTCTACGCCTA	576863	44	88
1161	13790	CACTGCTGGATGGAAAAAGA	576864	65	89
1196	13825	TGGTTTAAGGGCACAAACTC	576865	52	90
1231	13860	TTGCCCACGGGTACACAGCA	576866	63	91
1268	13897	CAGATGAGGAAATAGGTGTA	576867	62	92
1303	13932	ACACATTAGGTACTATTACT	576868	63	93
1372	14001	TTTTTATGTTCCAGGCACTG	576869	59	94
1407	14036	AATAGGAAATGTTAGCTATG	576870	30	95
1446	14075	GGCACTCAACAAATACTGGC	576871	72	96
1482	14111	TACATGTAAAGCAACTAGTA	576872	55	97
1539	14168	TAAAATTTCATGAAAATCTG	576873	0	98
1579	14208	AAGTGAATACTTTATACTTT	576874	0	99
1614	14243	CATCATGAGCCTAAAGGAAA	576875	51	100
1651	14280	GGCTCTTAGGTTAAACACAC	576876	43	101
1673	14302	TGCTTCTGATTCAAGCCATT	576877	65	102
1687	14316	ATACAGGACTAAAGTGCTTC	576878	74	103
1731	14360	CAAATGGGATTTAAAATGAT	576879	0	104
1766	14395	TGACATGTAGAGAGATTAAG	576880	26	105
1801	14430	TTATTGAAATACCATCATTT	576881	34	106
1836	14465	TAGTCAGTATAATATCATTT	576882	18	107

TABLE 7

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
851	n/a	GCATTGAGAAGAAAGCCTTC	571824	25	108
1337	n/a	AAGACCTGATCCAGGAAGGC	571836	53	109
861	n/a	TGAGCTGATGGCATTGAGAA	571981	41	110
890	14726	ACAACGGAACAGCCACAGGT	571983	66	111
1420	26405	TTAGTGTCAAGGCTTTTCTG	572007	60	112
75	1211	GACGGCTGACACACCAAGCG	576884	8	113
856	n/a	TGATGGCATTGAGAAGAAAG	576891	6	114
917	14753	TTTACTTTCTCTGCACTGCT	576892	68	115
922	n/a	TCTTATTTACTTTCTCTGCA	576893	63	116
940	16395	GGCATAATGTTCTGACTATC	576894	71	117
979	16434	ATAACCTGGAGCATTTTCTC	576895	65	118
1014	16469	CCCTGACTCATATTTAAATG	576896	70	119
1049	n/a	CCAGTTGAATCCTTTAGCAG	576897	51	120
1084	18233	CATACATGACTTGCCGGAAA	576898	66	121
1119	18268	GACATCCACATCTATGTGTG	576899	63	122
1154	18303	TGTTCATGACAGGGTGGCAT	576900	66	123
1163	18312	TTATAAATATGTTCATGACA	576901	51	124
1191	18340	CAGCTCGGATCTCATGTATC	576902	52	125
1205	18354	CTCCAGAAGGCTGTCAGCTC	576903	59	126
1238	18387	GTATCCTGAGCCATGTCTTC	576904	33	127
1273	18422	AATCAGGAGTAAAGCTTTCG	576905	48	128
1283	n/a	AAAATATTCAAATCAGGAGT	576906	23	129
1304	24306	TCTCTGTGTAAGACATCTTG	576907	51	130
1309	24311	GAGTGTCTCTGTGTAAGACA	576908	54	131
1314	24316	CACTAGAGTGTCTCTGTGTA	576909	50	132
1319	24321	GCTTTCACTAGAGTGTCTCT	576910	60	133
1330	24332	GATCCAGGAAGGCTTTCACT	576911	35	134
1373	26358	AAAGTACTTCTGAGAGATAA	576912	38	135
1385	26370	AACTGTGCAAGGAAAGTACT	576913	43	136
1415	26400	GTCAAGGCTTTTCTGTGAAG	576914	65	137
1472	26591	AGAGATTTAAAGGGCTTTTT	576915	46	138
1487	26606	ATCTTCAGGTTCCGAAGAGA	576916	53	139
1511	26630	CCCTCTGCTGTTAAATCAAG	576917	51	140
1522	26641	TGTTAAGATCGCCCTCTGCT	576918	64	141
1529	26648	ATTATTATGTTAAGATCGCC	576919	46	142
1535	26654	AGAGCCATTATTATGTTAAG	576920	36	143

TABLE 7-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
1571	26690	ATAAAAGAGTGTAGGCCTGG	576921	46	144
1598	26717	ACACTAGTGTAGAAAGGTCT	576922	55	145
1606	26725	GTTCTTGCACACTAGTGTAG	576923	62	146
1628	26747	TAAAAAGTCATTAGAACATC	576924	10	147
1644	26763	TATTAAGTTACACATTTAAA	576925	20	148
1679	26798	CTTTACCAGCGATCATGATT	576926	57	149
1725	26844	TTCTGGAGTATGATCCAGGG	576927	64	150
1752	24472 26871	ACTTAACTGCAATTGCTGAG	576928	66	151
1765	26884	TGTAGTGTAACTTACTTAAC	576929	60	152
1802	26921	ATGCACCTGACATCCCCTCA	576930	56	153
1844	26963	CCCAAAAGCATAAATCTAGG	576931	71	154
1876	24596 26995	ATATTTATTATATTGTAAAC	576932	0	155
1883	24603 27002	AGCAATAATATTTATTATAT	576933	1	156
1887	24607 27006	AGATAGCAATAATATTTATT	576934	0	157
1889	24609 27008	AAAGATAGCAATAATATTTA	576935	0	158
1892	24612 27011	TTAAAAGATAGCAATAATAT	576936	3	159
1896	24616 27015	ATCTTTAAAAGATAGCAATA	576937	14	160
1898	24618 27017	ATATCTTTAAAAGATAGCAA	576938	15	161
1901	24621 27020	ATTATATCTTTAAAAGATAG	576939	12	162
1905	24625 27024	TATTATTATATCTTTAAAAG	576940	6	163
1918	27037	CAAGTTTACATCCTATTATT	576941	48	164
1935	24655 27054	AAAACAGTAGTTGTGGTCAA	576942	77	165
1937	24657 27056	AAAAAACAGTAGTTGTGGTC	576943	69	166
1953	27072	TGAATCATGTATTTCAAAAA	576944	17	167
1988	27107	GCCAACTCAGATTTCACCTT	576945	71	168
2036	27155	CTACACACCAAAGAATGCCA	576946	69	169
2071	27190	AGTTTTCAGTTGATTGCAGA	576947	58	170
2127	27246	CATCCTATGTTCAAGCTCAC	576948	51	171
2162	27281	TAAACATCTGCTTGATCAAT	576949	44	172

TABLE 7-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
2197	27316	AATCCACAAAGTAGGATCTA	576950	42	173
2232	27351	ATTAGACATTTCTACAGACT	576951	56	174
2325	27444	CTCAACTACATAGAATATCA	576952	45	175
2371	27490	TTGGCAACAATTACTAAAAC	576953	48	176
2400	27519	TCAAAAATAATGAAAATTAA	576954	0	177
2409	27528	CAATTTGGCTCAAAAATAAT	576955	3	178
2429	27548	GGCACAGGAGGTGCACATTT	576956	60	179

TABLE 8

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
2451	27570	TAGATTTTCTAAGGAGAAAA	576957	8	180
2486	27605	ACTGACCAGTGAAATCTGAA	576958	50	181
2522	27641	GGTAAGACTTAGCAAGAAGA	576959	59	182
2557	27676	TCTCAGAGTTGCAATGATTG	576960	63	183
2597	27716	AGATCTTATTAGTTAGTATA	576961	18	184
2632	27751	AGTACTCAAGGAACTATTTT	576962	57	185
2679	27798	GGCAAACAGCAACAACTTCA	576963	71	186
2724	27843	GCACTTCAGTAAAATTTCTC	576964	69	187
2788	27907	GGTCCAAACGCATTAAGAAA	576965	58	188
2825	27944	GAATTATATTAATCAGTTAT	576966	0	189
2860	27979	TGTGTTTGTGTAACTACAAT	576967	67	190
2895	28014	ATATTACTTCCAGAATTTTA	576968	19	191
2949	28068	GGCAGAAGGGCTCTATTACC	576969	59	192
2992	28111	CATTCGAACATGTCATTTTG	576970	40	193
3027	28146	CTGATTCATGATGGGAAAGC	576971	34	194
3062	28181	GTGGTTGTCTAAAACATCAA	576972	58	195
3097	28216	ATGACTGAGCTACAGTACAA	576973	47	196
3132	28251	GGGACACTACAAGGTAGTAT	576974	56	197
3167	28286	TTAAATAAGAATCTACCATG	576975	12	198
3250	28369	GCTTTAATAACTTATTTCAC	576976	54	199
3282	28401	AGGAGAAAAGATATATAACA	576977	0	200
3288	28407	CCATTTAGGAGAAAAGATAT	576978	0	201
n/a	1343	TTCACCCTCAGCGAGTACTG	576979	0	202

TABLE 8-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
n/a	1403	AGGCTGCGGTTGTTTCCCTC	576980	0	203
n/a	1800	GCCAGATCCCCATCCCTTGT	576981	11	204
n/a	2187	TCACTTCCTTTAAGCAAGTC	576982	52	205
n/a	2209	AGTGATGCCCAAGTCACAAT	576983	53	206
n/a	2214	AGTCAAGTGATGCCCAAGTC	576984	47	207
n/a	2219	CCATCAGTCAAGTGATGCCC	576985	60	208
n/a	2224	GATTACCATCAGTCAAGTGA	576986	29	209
n/a	2229	CAACTGATTACCATCAGTCA	576987	42	210
n/a	2728	GCAGTTTCCAACTGATTCAG	576988	58	211
n/a	2760	CGTTCTTGTTTCAGATGTAC	576989	57	212
n/a	2862	GCCAAACAAAATATTTTATC	576990	22	213
n/a	2995	TAGGTAGGCTAACCTAGTCC	576991	47	214
n/a	3196	TCCCAGCCCAAAGAGAAGCA	576992	41	215
n/a	3466	GGATCATAGCTCTCGGTAAC	576993	26	216
n/a	3540	AATCATAAAGCCCTCACTTC	576994	7	217
n/a	3595	CTGATTGGTATTTAGAAAGG	576995	3	218
n/a	3705	ATGCAGACATGATTACATTA	576996	48	219
n/a	4560	TTCATCATTAAACTGAAAAT	576997	0	220
n/a	4613	CTTTTAGGTTAAAAAGGTGG	576998	35	221
n/a	4986	ATACAGAGCCTGGCAAAACA	576999	30	222
n/a	5036	TTCTATTTACAGAGCATTAG	577000	29	223
n/a	5656	GCCTTCACATTAATTCACCA	577001	62	224
n/a	6051	TGTGTTATTGCCCCTAAAAA	577002	24	225
n/a	6200	TGTATTCACTATACTATGCC	577003	52	226
n/a	6276	AAGTTATTTAAAGTATAGCA	577004	0	227
n/a	6762	GACATTGAAGTATCAAGACA	577005	34	228
n/a	6965	TGTTAAGTAATCTTAGAAAA	577006	0	229
n/a	7594	GGCATACATTTAGAAATTCA	577007	60	230
n/a	8309	ACCTTATGCATCCATATTCT	577008	59	231
n/a	8784	GAATTCTCTTGGGAACCATT	577009	42	232
n/a	8834	ATATTCAACTACAGGATTTA	577010	13	233
n/a	8884	ATGTGTTCTTTAGATACATC	577011	42	234
n/a	9510	CCTTATACAGATACATGCTG	577012	37	235
n/a	9663	TAGATGCAATTACTATTTTC	577013	34	236
n/a	10742	TGTACTTCCCAAACTTGAAC	577014	24	237
n/a	10845	CTGAAGCTCAACAACACCAA	577015	49	238

TABLE 8-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
n/a	11684	GTCTATAGAATCAAACTGAA	577016	38	239
n/a	11851	TTGAATCAATACCTAACCTC	577017	23	240
n/a	11991	TGCCTCTTTTAGAAAAGATC	577018	44	241
n/a	12042	ATGGAATCATTGGTTTATCG	577019	43	242
n/a	12069	AAAGCTCACTTTTATTCTTT	577020	37	243
n/a	12333				
n/a	12170	GGTGCCGCCACCATGCCCGG	577021	0	244
n/a	12464	GAGAGAAGCTGGGCAATAAA	577022	2	245
n/a	12514	TCTGACCCTGCACAATAAAG	577023	0	246
n/a	13016	ATAGTGTGTGATTCAAAACG	577024	17	247
n/a	13348	ACTGTATCAGCTATCTAAAA	577025	22	248
n/a	14540	TTATTTGTATAGGAACCTAC	577026	44	249
n/a	14699	TGTGAGCTGATGGCACTGTA	577027	61	250
n/a	14758	CCTTATTTACTTTCTCTGCA	577028	71	251
n/a	15587	GGAATAAGGTCACTAGTTCG	577029	69	252
n/a	17187	ATTTGCAACAATTTTTAAAT	577030	8	253
n/a	21808	ATAAACTACCAATGATATCC	577031	13	254
n/a	24337	TACCTGATCCAGGAAGGCTT	577032	40	255
n/a	24565	TTCCCGAAGCATAAATCTAG	577033	53	256
n/a	25549	TTGAGAAGCATGAAATTCCA	577034	48	257

TABLE 9

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
310	7990	GCCTTACTCTAGGACCAAGA	576816	90	40
75	1211	GACGGCTGACACACCAAGCG	576884	0	113
2	1138	GCGGGACACCGTAGGTTACG	577035	0	258
10	1146	CTTTCCTAGCGGGACACCGT	577036	1	259
18	1154	GCACCTCTCTTTCCTAGCGG	577037	0	260
26	1162	TGTTTGACGCACCTCTCTTT	577038	0	261
34	1170	CTTGTCGCTGTTTGACGCAC	577039	0	262
42	1178	GGGCGGAACTTGTCGCTGTT	577040	0	263
83	1219	GCAGCAGGGACGGCTGACAC	577041	0	264
95	1231	AGAAGCAACCGGGCAGCAGG	577042	0	265

TABLE 9-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
103	1239	CCCAAAAGAGAAGCAACCGG	577043	0	266
111	1247	ACCCCGCCCCCAAAAGAGAA	577044	1	267
119	1255	CTTGCTAGACCCCGCCCCCA	577045	0	268
127	1263	CACCTGCTCTTGCTAGACCC	577046	0	269
135	1271	TAAACCCACACCTGCTCTTG	577047	0	270
139	1275	CTCCTAAACCCACACCTGCT	577048	0	271
n/a	1283	ACACACACCTCCTAAACCCA	577049	0	272
n/a	1291	AAACAAAAACACACACCTCC	577050	5	273
n/a	1299	GGTGGGAAAAACAAAAACAC	577051	1	274
n/a	1326	CTGTGAGAGCAAGTAGTGGG	577052	3	275
n/a	1334	AGCGAGTACTGTGAGAGCAA	577053	0	276
n/a	1342	TCACCCTCAGCGAGTACTGT	577054	0	277
n/a	1358	TCAGGTCTTTTCTTGTTCAC	577055	0	278
n/a	1366	AATCTTTATCAGGTCTTTTC	577056	16	279
n/a	1374	TTCTGGTTAATCTTTATCAG	577057	22	280
n/a	1382	TTGTTTTCTTCTGGTTAATC	577058	19	281
n/a	1390	TTCCCTCCTTGTTTTCTTCT	577059	28	282
n/a	1398	GCGGTTGTTTCCCTCCTTGT	577060	17	283
n/a	1406	TACAGGCTGCGGTTGTTTCC	577061	28	284
n/a	1414	GAGCTTGCTACAGGCTGCGG	577062	23	285
n/a	1422	GAGTTCCAGAGCTTGCTACA	577063	14	286
n/a	1430	CGACTCCTGAGTTCCAGAGC	577064	0	287
n/a	1446	CCCGGCCCCTAGCGCGCGAC	577065	0	288
n/a	1454	GCCCCGGCCCCGGCCCCTAG	577066	0	289
n/a	1465	ACCACGCCCCGGCCCCGGCC	577067	0	290
n/a	1473	CCGCCCCGACCACGCCCCGG	577068	0	291
n/a	1481	CCCCGGGCCCGCCCCGACCA	577069	0	292
n/a	1495	CGCCCCGGGCCCGCCCCCGG	577070	0	293
n/a	1503	CGCAGCCCCGCCCCGGGCCC	577071	0	294
n/a	1511	ACCGCAACCGCAGCCCCGCC	577072	0	295
n/a	1519	GCGCAGGCACCGCAACCGCA	577073	18	296
n/a	1520	GGCGCAGGCACCGCAACCGC	577074	17	297
n/a	1536	CGCCTCCGCCGCCGCGGGCG	577075	32	298
n/a	1544	ACCGCCTGCGCCTCCGCCGC	577076	43	299
n/a	1552	CACTCGCCACCGCCTGCGCC	577077	52	300
n/a	1553	CCACTCGCCACCGCCTGCGC	577078	52	301

TABLE 9-continued

Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Sequence	ISIS No	% inhibition	SEQ ID NO
n/a	1853	GGTCCCCGGGAAGGAGACAG	577079	41	302
n/a	2453	AACAACTGGTGCATGGCAAC	577080	42	303
n/a	2753	GTTTCAGATGTACTATCAGC	577081	63	304
n/a	3053	AAGGTGAAGTTCATATCACT	577082	10	305
n/a	3452	GGTAACTTCAAACTCTTGGG	577083	70	306
n/a	3752	GGTTCATGAGAGGTTTCCCA	577084	53	307
n/a	4052	TACTGAATTGCTTAGTTTTA	577085	25	308
n/a	4425	CTAACAGAATAAGAAAAAAA	577086	0	309
n/a	5025	GAGCATTAGATGAGTGCTTT	577087	52	310
n/a	5325	TGCATTCCTAAGCAATGTGT	577088	28	311
n/a	5661	TCTAGGCCTTCACATTAATT	577089	37	312
n/a	5961	CCTGTCTATGCCTAGGTGAA	577090	19	313
n/a	6261	TAGCACATACAATTATTACA	577091	38	314
n/a	6566	GAGGAGAAGAACATAAACGC	577092	20	315
n/a	6866	TACCACAAGTCTGGAGCCAT	577093	27	316
n/a	7166	GATACTGGATTGTTGAAACT	577094	1	317
n/a	7466	TAGTATGACTGGAGATTTGG	577095	1	318
n/a	7766	ATCAAAACCCCAAATGATTT	577096	13	319
160	7840	ATCCAAATGCTCCGGAGATA	577097	78	320
190	7870	TCGACATCACTGCATTCCAA	577098	95	321
220	7900	CAACAGCTGGAGATGGCGGT	577099	56	322
250	7930	ATTTGCCACTTAAAGCAATC	577100	62	323
340	8020	GTACCTGTTCTGTCTTTGGA	577101	76	324
370	8050	CAAGAAAAGTTATTTCTCCA	577102	65	325
400	8080	GAAGGATTTCTCCATTTAGA	577103	50	326
430	8110	TTACATCTATAGCACCACTC	577104	73	327
460	8140	TCACTCCCTTTTCAGACAAG	577105	73	328
490	8170	AGTTTCCATCAAAGATTAAT	577106	55	329
520	8200	ATAGTCCATATGTGCTGCGA	577107	57	330
550	8230	AACTAAGTTCTGTCTGTGGA	577108	71	331
580	8260	CAACACACACTCTATGAAGT	577109	54	332
610	8290	TTCCTTTCCGGATTATATGT	577110	0	333

TABLE 10

Target SEQ ID NO	Target Start Site	ISIS No	Sequence	% inhibition	SEQ ID NO
3	751	576885	TTTCCATTACAGGAATCACT	63	334
3	807	576886	ATCAGCCTATATCTATTTCC	15	335
3	855	576887	TCAATGACCAGGCGGTCCCC	0	336
3	905	576888	CTTTTTATGGAAAAGGAAAA	0	337
3	984	576889	TGTTTCCCCAAAAATTTCTG	0	338
4	50	576890	AGATATCCACTCGCCACCGC	42	339

Example 2: Dose-Dependent Antisense Inhibition of Human C9ORF72 in HepG2 Cells

[0291] Antisense oligonucleotides from the study described above exhibiting significant in vitro inhibition of C9ORF72 mRNA were selected and tested at various doses in HepG2 cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 82.3 nM, 246.9 nM, 740.7 nM, 2,222.2 nM, 6,666.7 nM, or 20,000 nM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human C9ORF72 primer probe set RTS3750 was used to measure mRNA levels. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells.

[0292] The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented in Tables 11-13. As illustrated, C9ORF72 mRNA levels were reduced in a dose-dependent manner in the antisense oligonucleotide treated cells.

TABLE 11

ISIS No	82.3 nM	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM	IC_{50} (μM)
576816	5	23	49	76	91	96	0.9
576817	8	2	6	29	58	83	4.7
576818	0	22	31	68	87	90	1.4
576819	0	12	44	72	81	86	1.4
576820	18	24	52	78	91	93	0.7
576841	23	19	29	52	75	85	1.6
576842	6	12	13	37	53	83	4.1
576860	9	24	54	70	83	87	1.0
576878	1	9	26	61	77	83	2.0
576931	16	21	24	49	77	83	1.8
576942	6	16	26	57	78	85	1.8

TABLE 12

ISIS No	82.3 nM	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM	IC_{50} (μM)
576894	9	30	38	61	75	84	1.3
576896	17	17	28	47	66	76	2.5

TABLE 12-continued

ISIS No	82.3 nM	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM	IC_{50} (μM)
576927	3	26	40	60	79	81	1.5
576943	37	37	55	77	84	82	0.4
576945	20	41	56	73	83	84	0.6
576946	8	28	46	69	81	88	1.0
576963	0	0	25	51	63	83	2.9
576964	11	18	37	58	73	77	1.8
576967	19	31	48	68	77	85	0.9
577028	6	19	25	59	79	88	1.6
577029	7	22	44	67	77	85	1.3

TABLE 13

ISIS No	82.3 nM	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM	IC_{50} (μM)
576960	0	12	28	49	58	78	3.2
576974	25	45	65	70	65	78	0.5
576816	18	36	53	82	91	95	0.6
577097	22	20	31	63	82	94	1.1
577101	16	23	39	62	80	89	1.2
577105	0	4	30	48	78	92	2.0
577104	4	1	16	56	80	92	2.0
577108	0	0	24	52	76	83	2.9
577083	0	0	24	50	73	74	3.0
577078	0	0	10	15	30	75	10.8
577077	0	0	22	22	51	83	5.0

Example 3: Dose-Dependent Antisense Inhibition of Human C9ORF72 in HepG2 Cells

[0293] Antisense oligonucleotides from the study described above exhibiting significant in vitro inhibition of C9ORF72 mRNA were selected and tested at various doses in HepG2 cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 246.9 nM, 740.7 nM, 2,222.2 nM, 6,666.7 nM, or 20,000 nM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 total mRNA levels, as well as mRNA levels of the exon 1 transcript, were measured by quantitative real-time PCR. Human C9ORF72 primer probe set RTS3750 was used to measure total

C9ORF72 mRNA levels. Primer probe set RTS3905 (forward sequence GGGTCTAGCAAGAGCAGGTG, designated herein as SEQ ID NO: 18; reverse sequence GTCTTGGCAACAGCTGGAGAT, designated herein as SEQ ID NO: 19; probe sequence TGATGTCGACTCTTTGCCCACCGC, designated herein as SEQ ID NO: 20) was used to measure exon 1 message transcript. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells.

[0294] The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented in Tables 14 and 15. As illustrated, C9ORF72 mRNA levels were reduced in a dose-dependent manner in the antisense oligonucleotide treated cells. 'n.d.' indicates that there is no data for that particular dose.

TABLE 14

% inhibition of total C9ORF72 mRNA levels

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM	IC_{50} (μM)
576816	29	53	84	90	92	0.60
576820	20	42	70	87	75	1.19
576860	25	53	72	86	85	0.80
576974	36	49	64	65	68	0.95
577041	3	0	0	0	0	>20.00
577042	0	2	0	3	0	>20.00
577061	0	3	0	4	0	>20.00
577065	7	0	1	6	0	>20.00
577069	3	0	3	0	0	>20.00
577073	7	0	8	11	0	>20.00
577074	0	7	11	15	0	>20.00
577078	0	2	20	65	81	5.22
577083	0	19	55	71	75	3.35
577088	6	11	49	61	74	3.93
577097	3	38	62	78	82	1.94

TABLE 15

% inhibition of C9ORF72 exon 1 mRNA levels

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM	IC_{50} (μM)
576794	42	67	n.d.	93	87	0.27
576816	45	78	93	n.d.	n.d.	0.26
576820	54	65	92	98	94	<0.247
576860	43	36	71	95	91	0.66
577041	0	0	49	4	31	>20.00
577042	9	15	0	33	12	>20.00
577061	8	36	70	67	76	2.03
577065	20	55	67	82	62	1.06
577069	22	24	61	74	70	2.16
577073	4	62	69	82	81	1.21
577074	8	49	69	85	85	1.29
577078	0	21	59	81	n.d.	1.90
577083	30	43	85	88	92	0.71
577088	38	44	79	87	91	0.61
577097	17	47	52	94	89	1.27

Example 4: Antisense Inhibition of Human C9ORF72 in HepG2 Cells

[0295] Antisense oligonucleotides were designed targeting the hexanucleotide repeat expansion of a C9ORF72 nucleic acid and were tested for their effects on C9ORF72 mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. ISIS 576816 and ISIS 577065 were included in these assays for comparison. Cultured C9ORF72 fibroblasts at a density of 35,000 cells per well were transfected using electroporation with 7,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Human primer probe sets RTS3750, RTS 3905, or RTS4097 (forward sequence CAAGCCACCGTCTCACTCAA, designated herein as SEQ ID NO: 24; reverse sequence GTAGTGCTGTCTACTCCAGAGAGTTACC, designated herein as SEQ ID NO: 25; probe sequence CTTGGCTTCCCTCAAAAGACTGGCTAATGT, designated herein as SEQ ID NO: 26) were used to measure mRNA levels. RTS3750 targets exon 2 of the mRNA transcripts and, therefore, measures total mRNA transcripts. RTS3905 targets the hexanucleotide repeat expansion containing transcript and, therefore, measures only mRNA transcripts that contain the hexanucleotide repeat expansion. RTS4097 targets the gene sequence at a site 3' of the hexanucleotide repeat expansion. mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells. 'n.d.' indicates that there is no data for that particular antisense oligonucleotide.

[0296] The antisense oligonucleotides in Table 16 were designed as uniform MOE oligonucleotides, or 3-10-3 MOE, 4-10-3 MOE, 4-10-4 MOE, 5-10-4 MOE, or 5-10-5 MOE gapmers. The uniform MOE oligonucleotides are 20 nucleosides in length, wherein each nucleoside comprises a 2'-MOE group. The 3-10-3 MOE gapmers are 16 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising three nucleosides each. The 4-10-3 gapmers are 17 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising four and three nucleosides, respectively. The 4-10-4 gapmers are 18 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising four nucleosides each. The 5-10-4 gapmers are 19 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five and four nucleosides, respectively. The 5-10-5 gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment comprises a 2'-MOE group. The internucleoside linkages throughout each oligonucleotide are phosphorothioate linkages. All cytosine residues throughout each oligonucleotide are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted human gene sequence. Each antisense oligonucleotide listed in Table 16 is targeted to the human C9ORF72 genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_008413.18 truncated from

nucleosides 27535000 to 27565000) or SEQ ID NO: 13, which is an expanded version of the hexanucleotide repeat from intron 1 of the C9ORF72 gene.

[0297] The data indicates that certain antisense oligonucleotides preferentially inhibit levels of C9ORF72 mRNA transcript levels that contain the hexanucleotide repeat.

TABLE 16

Target Start Site on SEQ ID NO: 2	Target Start Site on SEQ ID NO: 13	Motif	Sequence	ISIS NO	% inhibition (RTS3750)	% inhibition (RTS3905)	% inhibition (RTS4097)	SEQ ID NO
1457	1 7 13	Uniform MOE	CCGGCCCCGGCCC CGGCCCC	573674	0	34	0	340
1458	2 8 14	Uniform MOE	CCCGGCCCCGGCC CCGGCCC	573675	0	28	0	341
1459	3 9 15	Uniform MOE	CCCCGGCCCCGGC CCCGGCC	573676	0	34	0	342
1460	4 10 16	Uniform MOE	GCCCCGGCCCCGG CCCCGGC	573677	4	41	0	343
n/a	5 11 17	Uniform MOE	GGCCCCGGCCCCG GCCCCGG	573678	12	11	6	344
n/a	6 12	Uniform MOE	CGGCCCCGGCCCC GGCCCCG	573679	0	0	0	345
1457	1 7 13	Uniform MOE	CGGCCCCGGCCCC GGCCCC	573680	10	6	0	346
1458	2 8 14	Uniform MOE	CCGGCCCCGGCCC CGGCCC	573681	13	23	0	347
1459	3 9 15	Uniform MOE	CCCGGCCCCGGCC CCGGCC	573682	2	48	0	348
1460	4 10 16	Uniform MOE	CCCCGGCCCCGGC CCCGGC	573683	0	38	0	349
1461	5 11 17	Uniform MOE	GCCCCGGCCCCGG CCCCGG	573684	0	0	0	350
n/a	6 12 18	Uniform MOE	GGCCCCGGCCCCG GCCCCG	573685	0	27	0	351
1457	1 7 13 19	Uniform MOE	GGCCCCGGCCCCG GCCCC	573686	0	40	0	352
1458	2 8 14	Uniform MOE	CGGCCCCGGCCCC GGCCC	573687	0	0	0	353
1459	3 9 15	Uniform MOE	CCGGCCCCGGCCC CGGCC	573688	22	0	0	354
1460	4 10 16	Uniform MOE	CCCGGCCCCGGCC CCGGC	573689	0	22	0	355
1461	5 11 17	Uniform MOE	CCCCGGCCCCGGC CCCGG	573690	15	43	0	356

TABLE 16-continued

Target Start Site on SEQ ID NO: 2	Target Start Site on SEQ ID NO: 13	Motif	Sequence	ISIS NO	% inhibition (RTS3750)	% inhibition (RTS3905)	% inhibition (RTS4097)	SEQ ID NO
1462	6	Uniform	GCCCCGGCCCCGG	573691	10	16	0	357
	12	MOE	CCCCG					
	18							
1457	1	Uniform	GCCCCGGCCCCGG	573692	6	65	0	358
	7	MOE	CCCC					
1463	13							
	19							
1458	2	Uniform	GGCCCCGGCCCCG	573693	9	0	0	359
	8	MOE	GCCC					
	14							
	20							
1459	3	Uniform	CGGCCCCGGCCCC	573694	10	0	0	360
	9	MOE	GGCC					
	15							
1460	4	Uniform	CCGGCCCCGGCCC	573695	3	42	0	361
	10	MOE	CGGC					
	16							
1461	5	Uniform	CCCGGCCCCGGCC	573696	0	23	0	362
	11	MOE	CCGG					
	17							
1462	6	Uniform	CCCCGGCCCCGGC	573697	0	28	0	363
	12	MOE	CCCG					
	18							
1457	1	Uniform	CCCCGGCCCCGGC	573698	1	68	0	364
	7	MOE	CCC					
1463	13							
	19							
1458	2	Uniform	GCCCCGGCCCCGG	573699	0	31	0	365
	8	MOE	CCC					
1464	14							
	20							
1459	3	Uniform	GGCCCCGGCCCCG	573700	7	2	2	366
	9	MOE	GCC					
	15							
	21							
1460	4	Uniform	CGGCCCCGGCCCC	573701	15	1	8	367
	10	MOE	GGC					
	16							
1461	5	Uniform	CCGGCCCCGGCCC	573702	26	0	0	368
	11	MOE	CGG					
	17							
1462	6	Uniform	CCCGGCCCCGGCC	573703	12	52	10	369
	12	MOE	CCG					
	18							
1457	1	5-10-5	CCGGCCCCGGCCC	573716	0	93	46	340
	7	MOE	CGGCCCC					
	13							
1458	2	5-10-5	CCCGGCCCCGGCC	573717	0	98	0	341
	8	MOE	CCGGCCC					
	14							
1459	3	5-10-5	CCCCGGCCCCGGC	573718	0	98	2	342
	9	MOE	CCCGGCC					
	15							

TABLE 16-continued

Target Start Site on SEQ ID NO: 2	Target Start Site on SEQ ID NO: 13	Motif	Sequence	ISIS NO	% inhibition (RTS3750)	% inhibition (RTS3905)	% inhibition (RTS4097)	SEQ ID NO
1460	4 10 16	5-10-5 MOE	GCCCCGGCCCCGG CCCCGGC	573719	0	68	19	343
n/a	5 11 17	5-10-5 MOE	GGCCCCGGCCCCG GCCCCGG	573720	13	90	18	344
n/a	6 12	5-10-5 MOE	CGGCCCCGGCCCC GGCCCCG	573721	0	98	18	345
1457	1 7 13	5-10-4 MOE	CGGCCCCGGCCCC GGCCCC	573722	0	97	0	346
1458	2 8 14	5-10-4 MOE	CCGGCCCCGGCCC CGGCCC	573723	0	n.d.	8	347
1459	3 9 15	5-10-4 MOE	CCCGGCCCCGGCC CCGGCC	573724	0	94	28	348
1460	4 10 16	5-10-4 MOE	CCCCGGCCCCGGC CCCGGC	573725	0	94	7	349
1461	5 11 17	5-10-4 MOE	GCCCCGGCCCCGG CCCCGG	573726	0	n.d.	28	350
n/a	6 12 18	5-10-4 MOE	GGCCCCGGCCCCG GCCCCG	573727	0	98	40	351
1457	1 7 13 19	4-10-4 MOE	GGCCCCGGCCCCG GCCCC	573728	0	97	19	352
1458	2 8 14	4-10-4 MOE	CGGCCCCGGCCCC GGCCC	573729	0	n.d.	36	353
1459	3 9 15	4-10-4 MOE	CCGGCCCCGGCCC CGGCC	573730	0	94	24	354
1460	4 10 16	4-10-4 MOE	CCCGGCCCCGGCC CCGGC	573731	0	97	13	355
1461	5 11 17	4-10-4 MOE	CCCCGGCCCCGGC CCCGG	573732	0	97	1	356
1462	6 12 18	4-10-4 MOE	GCCCCGGCCCCGG CCCCG	573733	0	n.d.	0	357
1457 1463	1 7 13 19	4-10-3 MOE	GCCCCGGCCCCGG CCCC	573734	0	96	0	358
1458	2 8 14 20	4-10-3 MOE	GGCCCCGGCCCCG GCCC	573735	0	94	21	359

TABLE 16-continued

Target Start Site on SEQ ID NO: 2	Target Start Site on SEQ ID NO: 13	Motif	Sequence	ISIS NO	% inhibition (RTS3750)	% inhibition (RTS3905)	% inhibition (RTS4097)	SEQ ID NO
1459	3 9 15	4-10-3 MOE	CGGCCCCGGCCCCGGCC	573736	0	93	43	360
1460	4 10 16	4-10-3 MOE	CCGGCCCCGGCCCCGGC	573737	0	96	19	361
1461	5 11 17	4-10-3 MOE	CCCGGCCCCGGCCCCGG	573738	0	n.d.	24	362
1462	6 12 18	4-10-3 MOE	CCCCGGCCCCGGCCCCG	573739	0	n.d.	34	363
1457 1463	1 7 13 19	3-10-3 MOE	CCCCGGCCCCGGCCCC	573740	0	n.d.	4	364
1458 1464	2 8 14 20	3-10-3 MOE	GCCCCGGCCCCGGCCC	573741	0	95	6	365
1459	3 9 15 21	3-10-3 MOE	GGCCCCGGCCCCGGCC	573742	23	97	49	366
1460	4 10 16	3-10-3 MOE	CGGCCCCGGCCCCGGC	573743	0	96	0	367
1461	5 11 17	3-10-3 MOE	CCGGCCCCGGCCCCGG	573744	0	94	34	368
1462	6 12 18	3-10-3 MOE	CCCGGCCCCGGCCCCG	573745	0	94	34	368
7990	n/a	5-10-5 MOE	GCCTTACTCTAGGACCAAGA	576816	83	91	29	40
1446	n/a	5-10-5 MOE	CCCGGCCCCTAGCGCGCGAC	577065	0	87	34	288

Example 5: In Vivo Rodent Inhibition and Tolerability with Treatment of C9ORF72 Antisense Oligonucleotides

[0298] In order to assess the tolerability of inhibition of C9ORF72 expression in vivo, antisense oligonucleotides targeting a murine C9ORF72 nucleic acid were designed and assessed in mouse and rat models.

[0299] ISIS 571883 was designed as a 5-10-5 MOE gapmer, 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a MOE modification. The internucleoside linkages are phosphorothioate linkages. All cytosine residues throughout the gapmer are 5-methylcytosines. ISIS 571883 has a target start site of nucleoside 33704 on the murine C9ORF72 genomic sequence, designated herein as SEQ ID NO: 11 (the complement of GENBANK Accession No. NT_166289.1 truncated from nucleosides 3587000 to 3625000).

[0300] ISIS 603538 was designed as a 5-10-5 MOE gapmer, 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on both the 5' end and on the 3' end comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a MOE modification. The internucleoside linkages are either phosphorothioate linkages or phosphate ester linkages (Gs Ao Co Co Gs Cs Ts Ts Gs As Gs Ts Ts Ts Gs Co Co Ao Cs A; wherein 's' denotes a phosphorothioate internucleoside linkage, 'o' denotes a phosphate ester linkage; and A, G, C, T denote the relevant nucleosides). All cytosine residues throughout the gapmer are 5-methylcytosines. ISIS 603538

has a target start site of nucleoside 2872 on the rat C9ORF72 mRNA sequence, designated herein as SEQ ID NO: 12 (GENBANK Accession No. NM_001007702.1).

Mouse Experiment 1

[0301] Groups of 4 C57BL/6 mice each were injected with 50 μg, 100 μg, 300 μg, 500 μg, or 700 μg of ISIS 571883 administered via an intracerebroventricular bolus injection. A control group of four C57/BL6 mice were similarly treated with PBS. Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. After sterilizing the surgical site, each mouse was injected −0.2 mm anterio-posterior from the bregma na d 3 mm dorsoventral to the bregma with the above-mentioned doses of ISIS 571883 using a Hamilton syringe. The incision was closed with sutures. The mice were allowed to recover for 14 days, after which animals were euthanized according to a humane protocol approved by the Institutional Animal Care and Use Committee. Brain and spinal cord tissue were harvested and snap frozen in liquid nitrogen. Prior to freezing, brain tissue was cut transversely five sections using a mouse brain matrix.

RNA Analysis

[0302] RNA was extracted from a 2-3 mm brain section posterior to the injection site, from brain frontal cortex and from the lumbar section of the spinal cord tissue for analysis of C9ORF72 mRNA expression. C9ORF72 mRNA expression was measured by RT-PCR. The data is presented in Table 17. The results indicate that treatment with increasing doses of ISIS 571883 resulted in dose-dependent inhibition of C9ORF72 mRNA expression.

[0303] The induction of the microglial marker AIF-1 as a measure of CNS toxicity was also assessed. The data is presented in Table 18. The results indicate that treatment with increasing doses of ISIS 571883 did not result in significant increases in AIF-1 mRNA expression. Hence, the injection of ISIS 571883 was deemed tolerable in this model.

TABLE 17

Percentage inhibition of C9ORF72 mRNA expression compared to the PBS control

Dose (μg)	Posterior brain	Cortex	Spinal cord
50	22	8	46
100	22	12	47
300	55	47	67
500	61	56	78
700	65	65	79

TABLE 18

Percentage expression of AIF-1 mRNA expression compared to the PBS control

Dose (μg)	Posterior brain	Spinal cord
50	102	89
100	105	111
300	107	98

TABLE 18-continued

Percentage expression of AIF-1 mRNA expression compared to the PBS control

Dose (μg)	Posterior brain	Spinal cord
500	131	124
700	122	116

Mouse Experiment 2

[0304] Groups of 4 C57BL/6 mice each were injected with 500 μg of ISIS 571883 administered via an intracerebroventricular bolus injection in a procedure similar to that described above. A control group of four C57/BL6 mice were similarly treated with PBS. The mice were tested at regular time points after ICV administration.

Behavior Analysis

[0305] Two standard assays to assess motor behavior were employed; the rotarod assay and grip strength assay. In case of the rotarod assays, the time of latency to fall was measured. The data for the assays is presented in Tables 19 and 20. The results indicate that there were no significant changes in the motor behavior of the mice as a result of antisense inhibition of ISIS 571883 or due to the ICV injection. Hence, antisense inhibition of C9ORF72 was deemed tolerable in this model.

TABLE 19

Latency to fall (sec) in the rotarod assay

Weeks after injection	PBS	ISIS 571883
0	66	66
4	91	70
8	94	84

TABLE 20

Mean hindlimb grip strength (g) in the grip strength assay

Weeks after injection	PBS	ISIS 571883
0	57	63
1	65	51
2	51	52
3	51	51
4	59	72
5	60	64
6	61	72
7	67	68
8	66	70
9	63	61
10	48	46

Rat Experiment

[0306] Groups of 4 Sprague-Dawley rats each were injected with 700 μg, 1,000 μg, or 3,000 μg of ISIS 603538 administered via an intrathecal bolus injection. A control group of four Sprague-Dawley rats were similarly treated with PBS. Animals were anesthetized with 3% isofluorane

and placed in a stereotactic frame. After sterilizing the surgical site, each rat was injected with 30 μL of ASO solution administered via 8 cm intrathecal catheter 2 cm into the spinal canal with a 50 μL flush. The rats were allowed to recover for 4 weeks, after which animals were euthanized according to a humane protocol approved by the Institutional Animal Care and Use Committee.

RNA Analysis

[0307] RNA was extracted from a 2-3 mm brain section posterior to the injection site, from brain frontal cortex, and from the cervical and lumbar sections of the spinal cord tissue for analysis of C9ORF72 mRNA expression. C9ORF72 mRNA expression was measured by RT-PCR. The data is presented in Table 21. The results indicate that treatment with increasing doses of ISIS 603538 resulted in dose-dependent inhibition of C9ORF72 mRNA expression.

[0308] The induction of the microglial marker AIF-1 as a measure of CNS toxicity was also assessed. The data is presented in Table 22. The results indicate that treatment with increasing doses of ISIS 603538 did not result in significant increases in AIF-1 mRNA expression. Hence, the injection of ISIS 603538 was deemed tolerable in this model.

TABLE 21

Percentage inhibition of C9ORF72 mRNA expression compared to the PBS control

Dose (μg)	Brain (1 mm section)	Cortex	Spinal cord (lumbar)	Spinal cord (cervical)
700	21	4	86	74
1000	53	49	88	82
3000	64	62	88	80

TABLE 22

Percentage expression of AIF-1 mRNA expression compared to the PBS control

Dose (μg)	Brain (1 mm section)	Cortex	Spinal cord (lumbar)	Spinal cord (cervical)
700	97	119	98	89
1000	105	113	122	96
3000	109	141	156	115

Body Weight Analysis

[0309] Body weights of the rats were measured at regular time point intervals. The data is presented in Table 23. The results indicate that treatment with increasing doses of ISIS 603538 did not have any significant changes in the body weights of the rats.

TABLE 23

Body weights of the rats (% initial body weight)

	Dose (μg)	Week 1	Week 2	Week 3	Week 4	Week 5
PBS		100	94	103	105	109
ISIS	700	100	94	98	103	107

TABLE 23-continued

Body weights of the rats (% initial body weight)

	Dose (μg)	Week 1	Week 2	Week 3	Week 4	Week 5
603538	1000	100	95	97	101	103
	3000	100	92	98	102	105

Example 6: Preferential Inhibition of Human C9ORF72 Expression in Two Patient Fibroblast Lines

[0310] Two different fibroblast cell lines from human patients (F09-152 and F09-229) were analyzed with antisense oligonucleotides that target the C9ORF72 pre-mRNA sequence before exon 1B; i.e. antisense oligonucleotides that target the hexanucleotide repeat expansion containing transcript and antisense oligonucleotides that target downstream of exon 1. The target start and stop sites and the target regions with respect to SEQ ID NOs: 1 and 2 for each oligonucleotide are provided in Table 24. ISIS 577061 and ISIS 577065 target C9ORF72 upstream of exon 1B and just upstream of the hexanucleotide repeat. The rest of the ISIS oligonucleotides of Table 24 target C9ORF72 downstream of exon 1B and the hexanucleotide repeat.

TABLE 24

Target Start and Stop sites of ISIS oligonucleotides used in a dose response assay in C9ORF72 patient fibroblasts

ISIS No	Target Start Site at SEQ ID NO: 1	Target Start Site at SEQ ID NO: 2	Target Region
577061	n/a	1406	Upstream of exon 1B
577065	n/a	1446	Upstream of exon 1B
577083	n/a	3452	Downstream of exon 1B
576816	232	7990	Exon 2
576974	3132	28251	Exon 11

[0311] Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 246.9 nM, 740.7 nM, 2,222.2 nM, 6,666.7 nM, and 20,000.0 nM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and C9ORF72 mRNA levels were measured by quantitative real-time PCR. Two primer probe sets were used: (1) human C9ORF72 primer probe set RTS3750, which measures total mRNA levels, and (2) RTS3905, which targets the hexanucleotide repeat expansion containing transcript, which measures only mRNA transcripts that contain the hexanucleotide repeat expansion. C9ORF72 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of C9ORF72, relative to untreated control cells.

[0312] As illustrated in Table 25, below, the two oligonucleotides that target upstream of exon 1B and, therefore, target mRNA transcripts containing the hexanucleotide repeat expansion (ISIS 577061 and ISIS 577065), do not inhibit total mRNA levels of C9ORF72 (as measured by

RTS3750) as well as ISIS 576974, 576816, and 577083, which target downstream of exon 1B and, therefore, do not target the mRNA transcript containing the hexanucleotide repeat expansion. Expression levels of the C9ORF72 mRNA transcript containing the hexanucleotide repeat expansion are low (about 10% of the total C9ORF72 expression products), therefore, oligonucleotides targeting the mRNA transcript containing the hexanucleotide repeat expansion do not robustly inhibit total C9ORF72 mRNA (as measured by RTS3905), as suggested by Table 25 below. Thus, ISIS 577061 and ISIS 577065 preferentially inhibit expression of mRNA transcripts containing the hexanucleotide repeat expansion.

TABLE 25

Percent inhibition of C9ORF72 total mRNA in F09-152 patient fibroblasts in a dose response assay as measured with RTS3750

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM
577061	6	11	0	18	10
577065	10	11	30	29	0
576974	61	69	72	83	83
576816	35	76	82	91	93
577083	28	38	52	75	80

TABLE 26

Percent inhibition of C9ORF72 mRNA transcripts containing the hexanucleotide repeat expansion in F09-152 patient fibroblasts in a dose response assay as measured with RTS3905

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM
577061	4	28	58	81	87
577065	25	54	70	90	94
576974	57	77	81	93	92

TABLE 26-continued

Percent inhibition of C9ORF72 mRNA transcripts containing the hexanucleotide repeat expansion in F09-152 patient fibroblasts in a dose response assay as measured with RTS3905

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM
576816	37	77	91	97	98
577083	37	53	74	93	94

TABLE 27

Percent inhibition of C9ORF72 total mRNA in F09-229 patient fibroblasts in a dose response assay as measured with RTS3750

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM
577061	0	0	0	17	7
577065	8	17	17	16	3
576974	43	58	85	85	74
576816	45	70	85	81	89
577083	22	45	56	76	78

TABLE 28

Percent inhibition of C9ORF72 mRNA transcripts containing the hexanucleotide repeat expansion in F09-229 patient fibroblasts in a dose response assay as measured with RTS3905

ISIS No	246.9 nM	740.7 nM	2222.2 nM	6666.7 nM	20000.0 nM
577061	14	36	70	87	89
577065	26	48	92	91	98
576974	63	87	91	92	91
576816	62	81	96	98	100
577083	36	64	82	98	96

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Gly Val Ile Ile Val Ser Leu Ile Phe Asp Gly Asn Trp Asn Gly Asp
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Arg Ser Thr Tyr Gly Leu Ser Ile Ile Leu Pro Gln Thr Glu Leu Ser
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Phe Tyr Leu Pro Leu His Arg Val Cys Val Asp Arg Leu Thr His Ile
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catggtaggt taaagctgtc atcttgctgt tttctatttg ttctttttgt tttctcctta 29700

cttttggatt tttttattct actatgtctt ttctattgtc ttattaacta tactctttga 29760

tttatttttag tggttgtttt agggttatac ctctttctaa tttaccagtt tataaccagt 29820

ttatatacta cttgacatat agcttaagaa acttactgtt gttgtctttt tgctgttatg 29880

gtcttaacgt ttttatttct acaaacatta taaactccac actttattgt tttttaattt 29940

tacttataca gtcaattatc ttttaaagat atttaaatat aaacattcaa aacaccccaa 30000

t 30001

<210> SEQ ID NO 3
<211> LENGTH: 1031
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

attcccggga tacgtaacct acggtgtccc gctaggaaag agaggtgcgt caaacagcga 60

caagttccgc ccacgtaaaa gatgacgctt ggtgtgtcag ccgtccctgc tgcccggttg 120

cttctctttt gggggcgggg tctagcaaga gcaggtgtgg gtttaggaga tatctccgga 180

gcatttggat aatgtgacag ttggaatgca gtgatgtcga ctctttgccc accgccatct 240

ccagctgttg ccaagacaga gattgcttta agtggcaaat caccttttatt agcagctact 300

tttgcttact gggacaatat tcttggtcct agagtaaggc acatttgggc tccaaagaca 360

gaacaggtac ttctcagtga tggagaaata acttttcttg ccaaccacac tctaaatgga 420

gaaatccttc gaaatgcaga gagtggtgct atagatgtaa agtttttgt cttgtctgaa 480

aagggagtga ttattgtttc attaatcttt gatggaaact ggaatgggga tcgcagcaca 540

tatggactat caattatact tccacagaca gaacttagtt tctacctccc acttcataga 600

gtgtgtgttg atagattaac acatataatc cggaaaggaa gaatatggat gcataaggaa 660

agacaagaaa aatgtccaga agattatctt agaaggcaca gagagaatgg aagatcaggg 720

tcagagtatt attccaatgc ttactggaga agtgattcct gtaatggaaa ctgctttcct 780

ctatgaaatt cccccgggtt cctggaggaa atagatatag gctgatacag ttacccaatg 840

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atggatgaat attgggggac cgcctggtca ttgaaaggct ttcttttctc caggaaagaa    900

atttttttcc ttttccataa aaagcttggg aatggaagac aacaattccc attcttttt    960

tgcgttccac ccctatgtga caacagaaat ttttggggaa acaacaacga aaaaatttta   1020

tcccgcgcgc a                                                       1031


<210> SEQ ID NO 4
<211> LENGTH: 3244
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (108)..(1553)

<400> SEQUENCE: 4

gggcggggct gcggttgcgg tgcctgcgcc cgcggcggcg gaggcgcagg cggtggcgag     60

tggatatctc cggagcattt ggataatgtg acagttggaa tgcagtg atg tcg act      116
                                                    Met Ser Thr
                                                    1

ctt tgc cca ccg cca tct cca gct gtt gcc aag aca gag att gct tta      164
Leu Cys Pro Pro Pro Ser Pro Ala Val Ala Lys Thr Glu Ile Ala Leu
    5                  10                  15

agt ggc aaa tca cct tta tta gca gct act ttt gct tac tgg gac aat      212
Ser Gly Lys Ser Pro Leu Leu Ala Ala Thr Phe Ala Tyr Trp Asp Asn
20                  25                  30                  35

att ctt ggt cct aga gta agg cac att tgg gct cca aag aca gaa cag      260
Ile Leu Gly Pro Arg Val Arg His Ile Trp Ala Pro Lys Thr Glu Gln
                40                  45                  50

gta ctt ctc agt gat gga gaa ata act ttt ctt gcc aac cac act cta      308
Val Leu Leu Ser Asp Gly Glu Ile Thr Phe Leu Ala Asn His Thr Leu
            55                  60                  65

aat gga gaa atc ctt cga aat gca gag agt ggt gct ata gat gta aag      356
Asn Gly Glu Ile Leu Arg Asn Ala Glu Ser Gly Ala Ile Asp Val Lys
        70                  75                  80

ttt ttt gtc ttg tct gaa aag gga gtg att att gtt tca tta atc ttt      404
Phe Phe Val Leu Ser Glu Lys Gly Val Ile Ile Val Ser Leu Ile Phe
    85                  90                  95

gat gga aac tgg aat ggg gat cgc agc aca tat gga cta tca att ata      452
Asp Gly Asn Trp Asn Gly Asp Arg Ser Thr Tyr Gly Leu Ser Ile Ile
100                 105                 110                 115

ctt cca cag aca gaa ctt agt ttc tac ctc cca ctt cat aga gtg tgt      500
Leu Pro Gln Thr Glu Leu Ser Phe Tyr Leu Pro Leu His Arg Val Cys
                120                 125                 130

gtt gat aga tta aca cat ata atc cgg aaa gga aga ata tgg atg cat      548
Val Asp Arg Leu Thr His Ile Ile Arg Lys Gly Arg Ile Trp Met His
            135                 140                 145

aag gaa aga caa gaa aat gtc cag aag att atc tta gaa ggc aca gag      596
Lys Glu Arg Gln Glu Asn Val Gln Lys Ile Ile Leu Glu Gly Thr Glu
        150                 155                 160

aga atg gaa gat cag ggt cag agt att att cca atg ctt act gga gaa      644
Arg Met Glu Asp Gln Gly Gln Ser Ile Ile Pro Met Leu Thr Gly Glu
    165                 170                 175

gtg att cct gta atg gaa ctg ctt tca tct atg aaa tca cac agt gtt      692
Val Ile Pro Val Met Glu Leu Leu Ser Ser Met Lys Ser His Ser Val
180                 185                 190                 195

cct gaa gaa ata gat ata gct gat aca gta ctc aat gat gat gat att      740
Pro Glu Glu Ile Asp Ile Ala Asp Thr Val Leu Asn Asp Asp Asp Ile
                200                 205                 210
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ggt gac agc tgt cat gaa ggc ttt ctt ctc aat gcc atc agc tca cac      788
Gly Asp Ser Cys His Glu Gly Phe Leu Leu Asn Ala Ile Ser Ser His
            215                 220                 225

ttg caa acc tgt ggc tgt tcc gtt gta gta ggt agc agt gca gag aaa      836
Leu Gln Thr Cys Gly Cys Ser Val Val Val Gly Ser Ser Ala Glu Lys
        230                 235                 240

gta aat aag ata gtc aga aca tta tgc ctt ttt ctg act cca gca gag      884
Val Asn Lys Ile Val Arg Thr Leu Cys Leu Phe Leu Thr Pro Ala Glu
    245                 250                 255

aga aaa tgc tcc agg tta tgt gaa gca gaa tca tca ttt aaa tat gag      932
Arg Lys Cys Ser Arg Leu Cys Glu Ala Glu Ser Ser Phe Lys Tyr Glu
260                 265                 270                 275

tca ggg ctc ttt gta caa ggc ctg cta aag gat tca act gga agc ttt      980
Ser Gly Leu Phe Val Gln Gly Leu Leu Lys Asp Ser Thr Gly Ser Phe
                280                 285                 290

gtg ctg cct ttc cgg caa gtc atg tat gct cca tat ccc acc aca cac     1028
Val Leu Pro Phe Arg Gln Val Met Tyr Ala Pro Tyr Pro Thr Thr His
            295                 300                 305

ata gat gtg gat gtc aat act gtg aag cag atg cca ccc tgt cat gaa     1076
Ile Asp Val Asp Val Asn Thr Val Lys Gln Met Pro Pro Cys His Glu
        310                 315                 320

cat att tat aat cag cgt aga tac atg aga tcc gag ctg aca gcc ttc     1124
His Ile Tyr Asn Gln Arg Arg Tyr Met Arg Ser Glu Leu Thr Ala Phe
    325                 330                 335

tgg aga gcc act tca gaa gaa gac atg gct cag gat acg atc atc tac     1172
Trp Arg Ala Thr Ser Glu Glu Asp Met Ala Gln Asp Thr Ile Ile Tyr
340                 345                 350                 355

act gac gaa agc ttt act cct gat ttg aat att ttt caa gat gtc tta     1220
Thr Asp Glu Ser Phe Thr Pro Asp Leu Asn Ile Phe Gln Asp Val Leu
                360                 365                 370

cac aga gac act cta gtg aaa gcc ttc ctg gat cag gtc ttt cag ctg     1268
His Arg Asp Thr Leu Val Lys Ala Phe Leu Asp Gln Val Phe Gln Leu
            375                 380                 385

aaa cct ggc tta tct ctc aga agt act ttc ctt gca cag ttt cta ctt     1316
Lys Pro Gly Leu Ser Leu Arg Ser Thr Phe Leu Ala Gln Phe Leu Leu
        390                 395                 400

gtc ctt cac aga aaa gcc ttg aca cta ata aaa tat ata gaa gac gat     1364
Val Leu His Arg Lys Ala Leu Thr Leu Ile Lys Tyr Ile Glu Asp Asp
    405                 410                 415

acg cag aag gga aaa aag ccc ttt aaa tct ctt cgg aac ctg aag ata     1412
Thr Gln Lys Gly Lys Lys Pro Phe Lys Ser Leu Arg Asn Leu Lys Ile
420                 425                 430                 435

gac ctt gat tta aca gca gag ggc gat ctt aac ata ata atg gct ctg     1460
Asp Leu Asp Leu Thr Ala Glu Gly Asp Leu Asn Ile Ile Met Ala Leu
                440                 445                 450

gct gag aaa att aaa cca ggc cta cac tct ttt atc ttt gga aga cct     1508
Ala Glu Lys Ile Lys Pro Gly Leu His Ser Phe Ile Phe Gly Arg Pro
            455                 460                 465

ttc tac act agt gtg caa gaa cga gat gtt cta atg act ttt taa         1553
Phe Tyr Thr Ser Val Gln Glu Arg Asp Val Leu Met Thr Phe
        470                 475                 480

atgtgtaact taataagcct attccatcac aatcatgatc gctggtaaag tagctcagtg   1613

gtgtggggaa acgttcccct ggatcatact ccagaattct gctctcagca attgcagtta   1673

agtaagttac actacagttc tcacaagagc ctgtgagggg atgtcaggtg catcattaca   1733

ttgggtgtct cttttcctag atttatgctt ttgggataca gacctatgtt tacaatataa   1793
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taaatattat tgctatcttt taaagatata ataataggat gtaaacttga ccacaactac 1853

tgtttttttg aaatacatga ttcatggttt acatgtgtca aggtgaaatc tgagttggct 1913

tttacagata gttgactttc tatcttttgg cattctttgg tgtgtagaat tactgtaata 1973

cttctgcaat caactgaaaa ctagagcctt taaatgattt caattccaca gaaagaaagt 2033

gagcttgaac ataggatgag ctttagaaag aaaattgatc aagcagatgt ttaattggaa 2093

ttgattatta gatcctactt tgtggattta gtccctggga ttcagtctgt agaaatgtct 2153

aatagttctc tatagtcctt gttcctggtg aaccacagtt agggtgtttt gtttatttta 2213

ttgttcttgc tattgttgat attctatgta gttgagctct gtaaaaggaa attgtatttt 2273

atgttttagt aattgttgcc aacttttaa attaattttc attatttttg agccaaattg 2333

aaatgtgcac ctcctgtgcc ttttttctcc ttagaaaatc taattacttg gaacaagttc 2393

agatttcact ggtcagtcat tttcatcttg ttttcttctt gctaagtctt accatgtacc 2453

tgctttggca atcattgcaa ctctgagatt ataaaatgcc ttagagaata tactaactaa 2513

taagatcttt ttttcagaaa cagaaaatag ttccttgagt acttccttct tgcatttctg 2573

cctatgtttt tgaagttgtt gctgtttgcc tgcaataggc tataaggaat agcaggagaa 2633

attttactga agtgctgttt tcctaggtgc tactttggca gagctaagtt atcttttgtt 2693

ttcttaatgc gtttggacca ttttgctggc tataaaataa ctgattaata taattctaac 2753

acaatgttga cattgtagtt acacaaacac aaataaatat tttatttaaa attctggaag 2813

taatataaaa gggaaaatat atttataaga aagggataaa ggtaatagag cccttctgcc 2873

ccccacccac caaatttaca caacaaaatg acatgttcga atgtgaaagg tcataatagc 2933

tttcccatca tgaatcagaa agatgtggac agcttgatgt tttagacaac cactgaacta 2993

gatgactgtt gtactgtagc tcagtcattt aaaaaatata taaatactac cttgtagtgt 3053

cccatactgt gttttttaca tggtagattc ttatttaagt gctaactggt tattttcttt 3113

ggctggttta ttgtactgtt atacagaatg taagttgtac agtgaaataa gttattaaag 3173

catgtgtaaa cattgttata tatcttttct cctaaatgga gaattttgaa taaaatatat 3233

ttgaaatttt g 3244

<210> SEQ ID NO 5
<211> LENGTH: 761
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (693)..(693)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (722)..(722)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 5

cacgaggctt tgatatttct tacaacgaat ttcatgtgta gacccactaa acagaagcta 60

taaaagttgc atggtcaaat aagtctgaga aagtctgcag atgatataat tcacctgaag 120

agtcacagta tgtagccaaa tgttaaaggt tttgagatgc catacagtaa atttaccaag 180

cattttctaa atttatttga ccacagaatc cctattttaa gcaacaactg ttacatccca 240

tggattccag gtgactaaag aatacttatt tcttaggata tgttttattg ataataacaa 300

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ttaaaatttc agatatcttt cataagcaaa tcagtggtct ttttacttca tgttttaatg    360

ctaaaatatt ttcttttata gatagtcaga acattatgcc tttttctgac tccagcagag    420

agaaaatgct ccaggttatg tgaagcagaa tcatcattta aatatgagtc agggctcttt    480

gtacaaggcc tgctaaagga ttcaactgga agctttgtgc tgcctttccg gcaagtcatg    540

tatgctccat atcccaccac acacatagat gtggatgtca atactgtgaa gcagatgcca    600

ccctgtcatg aacatattta taatcagcgt agatacatga gatccgagct gacagccttc    660

tggagagcca cttcagaaga agacatggct cangatacga tcatctacac tgacgaaagc    720

tntactcctg atttgaatat ttttcaagat gtcttacaca g                       761


<210> SEQ ID NO 6
<211> LENGTH: 1901
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (125)..(793)

<400> SEQUENCE: 6

acgtaaccta cggtgtcccg ctaggaaaga gaggtgcgtc aaacagcgac aagttccgcc     60

cacgtaaaag atgacgcttg atatctccgg agcatttgga taatgtgaca gttggaatgc    120

agtg atg tcg act ctt tgc cca ccg cca tct cca gct gtt gcc aag aca      169
     Met Ser Thr Leu Cys Pro Pro Pro Ser Pro Ala Val Ala Lys Thr
     1               5                  10                  15

gag att gct tta agt ggc aaa tca cct tta tta gca gct act ttt gct      217
Glu Ile Ala Leu Ser Gly Lys Ser Pro Leu Leu Ala Ala Thr Phe Ala
                20                  25                  30

tac tgg gac aat att ctt ggt cct aga gta agg cac att tgg gct cca      265
Tyr Trp Asp Asn Ile Leu Gly Pro Arg Val Arg His Ile Trp Ala Pro
            35                  40                  45

aag aca gaa cag gta ctt ctc agt gat gga gaa ata act ttt ctt gcc      313
Lys Thr Glu Gln Val Leu Leu Ser Asp Gly Glu Ile Thr Phe Leu Ala
        50                  55                  60

aac cac act cta aat gga gaa atc ctt cga aat gca gag agt ggt gct      361
Asn His Thr Leu Asn Gly Glu Ile Leu Arg Asn Ala Glu Ser Gly Ala
    65                  70                  75

ata gat gta aag ttt ttt gtc ttg tct gaa aag gga gtg att att gtt      409
Ile Asp Val Lys Phe Phe Val Leu Ser Glu Lys Gly Val Ile Ile Val
80                  85                  90                  95

tca tta atc ttt gat gga aac tgg aat ggg gat cgc agc aca tat gga      457
Ser Leu Ile Phe Asp Gly Asn Trp Asn Gly Asp Arg Ser Thr Tyr Gly
                100                 105                 110

cta tca att ata ctt cca cag aca gaa ctt agt ttc tac ctc cca ctt      505
Leu Ser Ile Ile Leu Pro Gln Thr Glu Leu Ser Phe Tyr Leu Pro Leu
            115                 120                 125

cat aga gtg tgt gtt gat aga tta aca cat ata atc cgg aaa gga aga      553
His Arg Val Cys Val Asp Arg Leu Thr His Ile Ile Arg Lys Gly Arg
        130                 135                 140

ata tgg atg cat aag gaa aga caa gaa aat gtc cag aag att atc tta      601
Ile Trp Met His Lys Glu Arg Gln Glu Asn Val Gln Lys Ile Ile Leu
    145                 150                 155

gaa ggc aca gag aga atg gaa gat cag ggt cag agt att att cca atg      649
Glu Gly Thr Glu Arg Met Glu Asp Gln Gly Gln Ser Ile Ile Pro Met
160                 165                 170                 175

ctt act gga gaa gtg att cct gta atg gaa ctg ctt tca tct atg aaa      697
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Leu Thr Gly Glu Val Ile Pro Val Met Glu Leu Leu Ser Ser Met Lys
                180                 185                 190

tca cac agt gtt cct gaa gaa ata gat ata gct gat aca gta ctc aat      745
Ser His Ser Val Pro Glu Glu Ile Asp Ile Ala Asp Thr Val Leu Asn
            195                 200                 205

gat gat gat att ggt gac agc tgt cat gaa ggc ttt ctt ctc aag taa      793
Asp Asp Asp Ile Gly Asp Ser Cys His Glu Gly Phe Leu Leu Lys
        210                 215                 220

gaatttttct tttcataaaa gctggatgaa gcagatacca tcttatgctc acctatgaca    853

agatttggaa gaaagaaaat aacagactgt ctacttagat tgttctaggg acattacgta    913

tttgaactgt tgcttaaatt tgtgttattt ttcactcatt atatttctat atatatttgg    973

tgttattcca tttgctattt aaagaaaccg agtttccatc ccagacaaga aatcatggcc   1033

ccttgcttga ttctggtttc ttgttttact tctcattaaa gctaacagaa tcctttcata   1093

ttaagttgta ctgtagatga acttaagtta tttaggcgta gaacaaaatt attcatattt   1153

atactgatct ttttccatcc agcagtggag tttagtactt aagagtttgt gcccttaaac   1213

cagactccct ggattaatgc tgtgtacccg tgggcaaggt gcctgaattc tctatacacc   1273

tatttcctca tctgtaaaat ggcaataata gtaatagtac ctaatgtgta gggttgttat   1333

aagcattgag taagataaat aatataaagc acttagaaca gtgcctggaa cataaaaaca   1393

cttaataata gctcatagct aacatttcct atttacattt cttctagaaa tagccagtat   1453

ttgttgagtg cctacatgtt agttccttta ctagttgctt tacatgtatt atcttatatt   1513

ctgttttaaa gtttcttcac agttacagat tttcatgaaa ttttactttt aataaaagag   1573

aagtaaaagt ataaagtatt cacttttatg ttcacagtct tttcctttag gctcatgatg   1633

gagtatcaga ggcatgagtg tgtttaacct aagagcctta atggcttgaa tcagaagcac   1693

tttagtcctg tatctgttca gtgtcagcct ttcatacatc attttaaatc ccatttgact   1753

ttaagtaagt cacttaatct ctctacatgt caatttcttc agctataaaa tgatggtatt   1813

tcaataaata aatacattaa ttaaatgata ttatactgac taattgggct gttttaaggc   1873

aaaaaaaaaa aaaaaaaaaa aaaaaaaa                                      1901

<210> SEQ ID NO 7
<211> LENGTH: 562
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (166)..(166)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 7

agacgtaacc tacggtgtcc cgctaggaaa gagagatatc tccggagcat ttggataatg     60

tgacagttgg aatgcagtga tgtcgactct ttgcccaccg ccatctccag ctgttgccaa    120

gacagagatt gctttaagtg gcaaatcacc tttattagca gctacntttt gcttactggg    180

acaatattct tggtcctaga gtaaggcaca tttgggctcc aaagacagaa caggtacttc    240

tcagtgatgg agaaataact tttcttgcca accacactct aaatggagaa atccttcgaa    300

atgcagagag tggtgctata gatgtaaagt tttttgtctt gtctgaaaag ggagtgatta    360

ttgtttcatt aatctttgat ggaaactgga atggggatcg cagcacatat ggactatcaa    420

ttatacttcc acagacagaa cttagtttct acctcccact tcatagagtg tgtgttgata    480
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gattaacaca tataatccgg aaaggaagaa tatggatgca taaggaaaga caagaaaatg    540

tccagaagat tatcttagaa gg                                            562


<210> SEQ ID NO 8
<211> LENGTH: 798
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (81)..(590)

<400> SEQUENCE: 8

gggctctctt ttgggggcgg ggtctagcaa gagcagatat ctccggagca tttggataat     60

gtgacagttg gaatgcagtg atg tcg act ctt tgc cca ccg cca tct cca gct    113
                    Met Ser Thr Leu Cys Pro Pro Pro Ser Pro Ala
                    1               5                   10

gtt gcc aag aca gag att gct tta agt ggc aaa tca cct tta tta gca      161
Val Ala Lys Thr Glu Ile Ala Leu Ser Gly Lys Ser Pro Leu Leu Ala
            15                  20                  25

gct act ttt gct tac tgg gac aat att ctt ggt cct aga gta agg cac      209
Ala Thr Phe Ala Tyr Trp Asp Asn Ile Leu Gly Pro Arg Val Arg His
        30                  35                  40

att tgg gct cca aag aca gaa cag gta ctt ctc agt gat gga gaa ata      257
Ile Trp Ala Pro Lys Thr Glu Gln Val Leu Leu Ser Asp Gly Glu Ile
    45                  50                  55

act ttt ctt gcc aac cac act cta aat gga gaa atc ctt cga aat gca      305
Thr Phe Leu Ala Asn His Thr Leu Asn Gly Glu Ile Leu Arg Asn Ala
60                  65                  70                  75

gag agt ggt gct ata gat gta aag ttt ttt gtc ttg tct gaa aag gga      353
Glu Ser Gly Ala Ile Asp Val Lys Phe Phe Val Leu Ser Glu Lys Gly
                80                  85                  90

gtg att att gtt tca tta atc ttt gat gga aac tgg aat ggg gat cgc      401
Val Ile Ile Val Ser Leu Ile Phe Asp Gly Asn Trp Asn Gly Asp Arg
            95                  100                 105

agc aca tat gga cta tca att ata ctt cca cag aca gaa ctt agt ttc      449
Ser Thr Tyr Gly Leu Ser Ile Ile Leu Pro Gln Thr Glu Leu Ser Phe
        110                 115                 120

tac ctc cca ctt cat aga gtg tgt gtt gat aga tta aca cat ata atc      497
Tyr Leu Pro Leu His Arg Val Cys Val Asp Arg Leu Thr His Ile Ile
    125                 130                 135

cgg aaa gga aga ata tgg atg cat aag gaa aga caa gaa aat gtc cag      545
Arg Lys Gly Arg Ile Trp Met His Lys Glu Arg Gln Glu Asn Val Gln
140                 145                 150                 155

aag att atc tta gaa ggc aca gag aga atg gaa gat cag ggt cag          590
Lys Ile Ile Leu Glu Gly Thr Glu Arg Met Glu Asp Gln Gly Gln
                160                 165                 170

agtattattc caatgcttac tggagaagtg attcctgtaa tgggactgct ttcatctatg    650

aaatcacaca gtgttcctga agaaatagat atagctgata cagtactcca tgatgatgat    710

atttggtgac agctgtcatg aaaggctttc ttctcaagta ggaatttttt cttttcataa    770

aagctgggat gaagccagat tcccatct                                       798

<210> SEQ ID NO 9
<211> LENGTH: 169
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9
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aaacagcgac aagttccgcc cacgtaaaag atgatgcttg gtgtgtcagc cgtccctgct 60

gcccggttgc ttctcttttg ggggcggggt ctagcaagag cagatatctc cggagcattt 120

ggataatgtg acagttggaa tgcggtgatg tcgactcttt gcccaccgc 169

<210> SEQ ID NO 10
<211> LENGTH: 176
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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tat ccc acc aca cac atc gat gtg gat gtc aac act gtc aag cag atg     1323
Tyr Pro Thr Thr His Ile Asp Val Asp Val Asn Thr Val Lys Gln Met
        305                 310                 315

cca ccg tgt cat gaa cat att tat aat caa cgc aga tac atg agg tca     1371
Pro Pro Cys His Glu His Ile Tyr Asn Gln Arg Arg Tyr Met Arg Ser
    320                 325                 330

gag ctg aca gcc ttc tgg agg gca act tca gaa gag gac atg gct cag     1419
Glu Leu Thr Ala Phe Trp Arg Ala Thr Ser Glu Glu Asp Met Ala Gln
335                 340                 345                 350

gac acc atc atc tac aca gat gag agc ttc act cct gat ttg aat att     1467
Asp Thr Ile Ile Tyr Thr Asp Glu Ser Phe Thr Pro Asp Leu Asn Ile
                355                 360                 365

ttc caa gat gtc tta cac aga gac act cta gtg aaa gcc ttt ctg gat     1515
Phe Gln Asp Val Leu His Arg Asp Thr Leu Val Lys Ala Phe Leu Asp
            370                 375                 380

cag gtc ttc cat ttg aag cct ggc ctg tct ctc agg agt act ttc ctt     1563
Gln Val Phe His Leu Lys Pro Gly Leu Ser Leu Arg Ser Thr Phe Leu
        385                 390                 395

gca cag ttc ctc ctc att ctt cac aga aaa gcc ttg aca cta atc aag     1611
Ala Gln Phe Leu Leu Ile Leu His Arg Lys Ala Leu Thr Leu Ile Lys
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tac ata gag gat gac acg cag aag ggg aaa aag ccc ttt aag tct ctt     1659
Tyr Ile Glu Asp Asp Thr Gln Lys Gly Lys Lys Pro Phe Lys Ser Leu
415                 420                 425                 430

cgg aac ctg aag ata gat ctt gat tta aca gca gag ggc gac ctt aac     1707
Arg Asn Leu Lys Ile Asp Leu Asp Leu Thr Ala Glu Gly Asp Leu Asn
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ata ata atg gct cta gct gag aaa att aag cca ggc cta cac tct ttc     1755
Ile Ile Met Ala Leu Ala Glu Lys Ile Lys Pro Gly Leu His Ser Phe
            450                 455                 460

atc ttc ggg aga cct ttc tac act agt gtc caa gaa cgt gat gtt cta     1803
Ile Phe Gly Arg Pro Phe Tyr Thr Ser Val Gln Glu Arg Asp Val Leu
        465                 470                 475

atg act ttt taa acatgtggtt tgctccgtgt gtctcatgac agtcacactt         1855
Met Thr Phe
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gctgttacag tgtctcagcg ctttggacac atccttcctc cagggtcctg ccgcaggaca   1915
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gtcacattat ccaaatgctc 20

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aaaagttatt tctccatcac 20

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agtataattg atagtccata 20

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atgtgttaat ctatcaacac 20

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ataatcttct ggacattttc 20

<210> SEQ ID NO 66
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ctctgaccct gatcttccat 20

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cagttccatt acaggaatca 20

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cttcaggaac actgtgtgat 20

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atctatttct tcaggaacac 20

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agtactgtat cagctatatc 20

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tcattgagta ctgtatcagc 20

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tcatcatcat tgagtactgt 20

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ccaatatcat catcattgag 20

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tcatgacagc tgtcaccaat 20

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aagccttcat gacagctgtc 20

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agaagaaagc cttcatgaca 20

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tacttgagaa gaaagccttc 20

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agatggtatc tgcttcatcc 20

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caatctaagt agacagtctg 20

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<212> TYPE: DNA
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<400> SEQUENCE: 83

ttaagcaaca gttcaaatac 20

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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 84

ctttaaatag caaatggaat 20

<210> SEQ ID NO 85
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 85

gccatgattt cttgtctggg 20

<210> SEQ ID NO 86
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 86

gctttaatga gaagtaaaac 20

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<400> SEQUENCE: 87

tctacagtac aacttaatat 20

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ataattttgt tctacgccta 20

<210> SEQ ID NO 89
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cactgctgga tggaaaaaga 20

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tggtttaagg gcacaaactc 20

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ttgcccacgg gtacacagca 20

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 92

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cagatgagga aataggtgta 20

<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 93

acacattagg tactattact 20

<210> SEQ ID NO 94
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 94

tttttatgtt ccaggcactg 20

<210> SEQ ID NO 95
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 95

aataggaaat gttagctatg 20

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 96

ggcactcaac aaatactggc 20

<210> SEQ ID NO 97
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 97

tacatgtaaa gcaactagta 20

<210> SEQ ID NO 98
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 98

taaaatttca tgaaaatctg 20

<210> SEQ ID NO 99

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
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<400> SEQUENCE: 99

aagtgaatac tttatacttt 20

<210> SEQ ID NO 100
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
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<400> SEQUENCE: 100

catcatgagc ctaaaggaaa 20

<210> SEQ ID NO 101
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 101

ggctcttagg ttaaacacac 20

<210> SEQ ID NO 102
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 102

tgcttctgat tcaagccatt 20

<210> SEQ ID NO 103
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 103

atacaggact aaagtgcttc 20

<210> SEQ ID NO 104
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 104

caaatgggat ttaaaatgat 20

<210> SEQ ID NO 105
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

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tgacatgtag agagattaag 20

<210> SEQ ID NO 106
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<212> TYPE: DNA
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<400> SEQUENCE: 106

ttattgaaat accatcattt 20

<210> SEQ ID NO 107
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<212> TYPE: DNA
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tagtcagtat aatatcattt 20

<210> SEQ ID NO 108
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<212> TYPE: DNA
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gcattgagaa gaaagccttc 20

<210> SEQ ID NO 109
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 109

aagacctgat ccaggaaggc 20

<210> SEQ ID NO 110
<211> LENGTH: 20
<212> TYPE: DNA
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tgagctgatg gcattgagaa 20

<210> SEQ ID NO 111
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acaacggaac agccacaggt 20

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<400> SEQUENCE: 112

ttagtgtcaa ggcttttctg 20

<210> SEQ ID NO 113
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

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gacggctgac acaccaagcg 20

<210> SEQ ID NO 114
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 114

tgatggcatt gagaagaaag 20

<210> SEQ ID NO 115
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 115

tttactttct ctgcactgct 20

<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 116

tcttatttac tttctctgca 20

<210> SEQ ID NO 117
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 117

ggcataatgt tctgactatc 20

<210> SEQ ID NO 118

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 118

ataacctgga gcattttctc 20

<210> SEQ ID NO 119
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 119

ccctgactca tatttaaatg 20

<210> SEQ ID NO 120
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 120

ccagttgaat cctttagcag 20

<210> SEQ ID NO 121
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 121

catacatgac ttgccggaaa 20

<210> SEQ ID NO 122
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 122

gacatccaca tctatgtgtg 20

<210> SEQ ID NO 123
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 123

tgttcatgac agggtggcat 20

<210> SEQ ID NO 124
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 124

ttataaatat gttcatgaca 20

<210> SEQ ID NO 125
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 125

cagctcggat ctcatgtatc 20

<210> SEQ ID NO 126
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 126

ctccagaagg ctgtcagctc 20

<210> SEQ ID NO 127
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 127

gtatcctgag ccatgtcttc 20

<210> SEQ ID NO 128
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 128

aatcaggagt aaagctttcg 20

<210> SEQ ID NO 129
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 129

aaaatattca aatcaggagt 20

<210> SEQ ID NO 130
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 130

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tctctgtgta agacatcttg 20

<210> SEQ ID NO 131
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 131

gagtgtctct gtgtaagaca 20

<210> SEQ ID NO 132
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 132

cactagagtg tctctgtgta 20

<210> SEQ ID NO 133
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 133

gctttcacta gagtgtctct 20

<210> SEQ ID NO 134
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 134

gatccaggaa ggctttcact 20

<210> SEQ ID NO 135
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 135

aaagtacttc tgagagataa 20

<210> SEQ ID NO 136
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 136

aactgtgcaa ggaaagtact 20

<210> SEQ ID NO 137

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 137

gtcaaggctt ttctgtgaag 20

<210> SEQ ID NO 138
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 138

agagatttaa agggcttttt 20

<210> SEQ ID NO 139
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 139

atcttcaggt tccgaagaga 20

<210> SEQ ID NO 140
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 140

ccctctgctg ttaaatcaag 20

<210> SEQ ID NO 141
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 141

tgttaagatc gccctctgct 20

<210> SEQ ID NO 142
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 142

attattatgt taagatcgcc 20

<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 143

agagccatta ttatgttaag 20

<210> SEQ ID NO 144
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 144

ataaaagagt gtaggcctgg 20

<210> SEQ ID NO 145
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 145

acactagtgt agaaaggtct 20

<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 146

gttcttgcac actagtgtag 20

<210> SEQ ID NO 147
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 147

taaaaagtca ttagaacatc 20

<210> SEQ ID NO 148
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 148

tattaagtta cacatttaaa 20

<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 149

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ctttaccagc gatcatgatt 20

<210> SEQ ID NO 150
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 150

ttctggagta tgatccaggg 20

<210> SEQ ID NO 151
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 151

acttaactgc aattgctgag 20

<210> SEQ ID NO 152
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 152

tgtagtgtaa cttacttaac 20

<210> SEQ ID NO 153
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 153

atgcacctga catcccctca 20

<210> SEQ ID NO 154
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 154

cccaaaagca taaatctagg 20

<210> SEQ ID NO 155
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 155

atatttatta tattgtaaac 20

<210> SEQ ID NO 156

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 156

agcaataata tttattatat 20

<210> SEQ ID NO 157
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 157

agatagcaat aatatttatt 20

<210> SEQ ID NO 158
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 158

aaagatagca ataatattta 20

<210> SEQ ID NO 159
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 159

ttaaaagata gcaataatat 20

<210> SEQ ID NO 160
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 160

atctttaaaa gatagcaata 20

<210> SEQ ID NO 161
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 161

atatctttaa aagatagcaa 20

<210> SEQ ID NO 162
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 162

attatatctt taaaagatag 20

<210> SEQ ID NO 163
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 163

tattattata tctttaaaag 20

<210> SEQ ID NO 164
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 164

caagtttaca tcctattatt 20

<210> SEQ ID NO 165
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 165

aaaacagtag ttgtggtcaa 20

<210> SEQ ID NO 166
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 166

aaaaaacagt agttgtggtc 20

<210> SEQ ID NO 167
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 167

tgaatcatgt atttcaaaaa 20

<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 168

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gccaactcag atttcacctt 20

<210> SEQ ID NO 169
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 169

ctacacacca aagaatgcca 20

<210> SEQ ID NO 170
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 170

agttttcagt tgattgcaga 20

<210> SEQ ID NO 171
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 171

catcctatgt tcaagctcac 20

<210> SEQ ID NO 172
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 172

taaacatctg cttgatcaat 20

<210> SEQ ID NO 173
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 173

aatccacaaa gtaggatcta 20

<210> SEQ ID NO 174
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 174

attagacatt tctacagact 20

<210> SEQ ID NO 175

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 175

ctcaactaca tagaatatca 20

<210> SEQ ID NO 176
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 176

ttggcaacaa ttactaaaac 20

<210> SEQ ID NO 177
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 177

tcaaaaataa tgaaaattaa 20

<210> SEQ ID NO 178
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 178

caatttggct caaaaataat 20

<210> SEQ ID NO 179
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 179

ggcacaggag gtgcacattt 20

<210> SEQ ID NO 180
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 180

tagattttct aaggagaaaa 20

<210> SEQ ID NO 181
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 181

actgaccagt gaaatctgaa 20

<210> SEQ ID NO 182
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 182

ggtaagactt agcaagaaga 20

<210> SEQ ID NO 183
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 183

tctcagagtt gcaatgattg 20

<210> SEQ ID NO 184
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 184

agatcttatt agttagtata 20

<210> SEQ ID NO 185
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 185

agtactcaag gaactatttt 20

<210> SEQ ID NO 186
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 186

ggcaaacagc aacaacttca 20

<210> SEQ ID NO 187
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 187

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gcacttcagt aaaatttctc 20

<210> SEQ ID NO 188
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 188

ggtccaaacg cattaagaaa 20

<210> SEQ ID NO 189
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 189

gaattatatt aatcagttat 20

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<220> FEATURE:
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tgtgtttgtg taactacaat 20

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atattacttc cagaatttta 20

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ggcagaaggg ctctattacc 20

<210> SEQ ID NO 193
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cattcgaaca tgtcattttg 20

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ctgattcatg atgggaaagc 20

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gtggttgtct aaaacatcaa 20

<210> SEQ ID NO 196
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atgactgagc tacagtacaa 20

<210> SEQ ID NO 197
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gggacactac aaggtagtat 20

<210> SEQ ID NO 198
<211> LENGTH: 20
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ttaaataaga atctaccatg 20

<210> SEQ ID NO 199
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gctttaataa cttatttcac 20

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<223> OTHER INFORMATION: Synthetic oligonucleotide

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aggagaaaag atatataaca 20

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ccatttagga gaaaagatat 20

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ttcaccctca gcgagtactg 20

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aggctgcggt tgtttccctc 20

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gccagatccc catcccttgt 20

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tcacttcctt taagcaagtc 20

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agtgatgccc aagtcacaat 20

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agtcaagtga tgcccaagtc 20

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ccatcagtca agtgatgccc 20

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gattaccatc agtcaagtga 20

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caactgatta ccatcagtca 20

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gcagtttcca actgattcag 20

<210> SEQ ID NO 212
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cgttcttgtt tcagatgtac 20

<210> SEQ ID NO 213

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<400> SEQUENCE: 213

gccaaacaaa atattttatc 20

<210> SEQ ID NO 214
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<400> SEQUENCE: 214

taggtaggct aacctagtcc 20

<210> SEQ ID NO 215
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tcccagccca aagagaagca 20

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<400> SEQUENCE: 216

ggatcatagc tctcggtaac 20

<210> SEQ ID NO 217
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<400> SEQUENCE: 217

aatcataaag ccctcacttc 20

<210> SEQ ID NO 218
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 218

ctgattggta tttagaaagg 20

<210> SEQ ID NO 219
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 219

atgcagacat gattacatta 20

<210> SEQ ID NO 220
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 220

ttcatcatta aactgaaaat 20

<210> SEQ ID NO 221
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 221

cttttaggtt aaaaaggtgg 20

<210> SEQ ID NO 222
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 222

atacagagcc tggcaaaaca 20

<210> SEQ ID NO 223
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 223

ttctatttac agagcattag 20

<210> SEQ ID NO 224
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 224

gccttcacat taattcacca 20

<210> SEQ ID NO 225
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 225

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tgtgttattg cccctaaaaa 20

<210> SEQ ID NO 226
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 226

tgtattcact atactatgcc 20

<210> SEQ ID NO 227
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 227

aagttattta aagtatagca 20

<210> SEQ ID NO 228
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 228

gacattgaag tatcaagaca 20

<210> SEQ ID NO 229
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 229

tgttaagtaa tcttagaaaa 20

<210> SEQ ID NO 230
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 230

ggcatacatt tagaaattca 20

<210> SEQ ID NO 231
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 231

accttatgca tccatattct 20

<210> SEQ ID NO 232

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<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 232

gaattctctt gggaaccatt 20

<210> SEQ ID NO 233
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 233

atattcaact acaggattta 20

<210> SEQ ID NO 234
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 234

atgtgttctt tagatacatc 20

<210> SEQ ID NO 235
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 235

ccttatacag atacatgctg 20

<210> SEQ ID NO 236
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 236

tagatgcaat tactattttc 20

<210> SEQ ID NO 237
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 237

tgtacttccc aaacttgaac 20

<210> SEQ ID NO 238
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 238

ctgaagctca acaacaccaa 20

<210> SEQ ID NO 239
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 239

gtctatagaa tcaaactgaa 20

<210> SEQ ID NO 240
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 240

ttgaatcaat acctaacctc 20

<210> SEQ ID NO 241
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 241

tgcctctttt agaaaagatc 20

<210> SEQ ID NO 242
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 242

atggaatcat tggtttatcg 20

<210> SEQ ID NO 243
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 243

aaagctcact tttattcttt 20

<210> SEQ ID NO 244
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 244

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ggtgccgcca ccatgcccgg 20

<210> SEQ ID NO 245
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 245

gagagaagct gggcaataaa 20

<210> SEQ ID NO 246
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 246

tctgaccctg cacaataaag 20

<210> SEQ ID NO 247
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 247

atagtgtgtg attcaaaacg 20

<210> SEQ ID NO 248
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 248

actgtatcag ctatctaaaa 20

<210> SEQ ID NO 249
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 249

ttatttgtat aggaacctac 20

<210> SEQ ID NO 250
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 250

tgtgagctga tggcactgta 20

<210> SEQ ID NO 251

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 251

ccttatttac tttctctgca 20

<210> SEQ ID NO 252
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 252

ggaataaggt cactagttcg 20

<210> SEQ ID NO 253
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 253

atttgcaaca atttttaaat 20

<210> SEQ ID NO 254
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 254

ataaactacc aatgatatcc 20

<210> SEQ ID NO 255
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 255

tacctgatcc aggaaggctt 20

<210> SEQ ID NO 256
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 256

ttcccgaagc ataaatctag 20

<210> SEQ ID NO 257
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 257

ttgagaagca tgaaattcca 20

<210> SEQ ID NO 258
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 258

gcgggacacc gtaggttacg 20

<210> SEQ ID NO 259
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 259

ctttcctagc gggacaccgt 20

<210> SEQ ID NO 260
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 260

gcacctctct ttcctagcgg 20

<210> SEQ ID NO 261
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 261

tgtttgacgc acctctcttt 20

<210> SEQ ID NO 262
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 262

cttgtcgctg tttgacgcac 20

<210> SEQ ID NO 263
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 263

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gggcggaact tgtcgctgtt 20

<210> SEQ ID NO 264
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 264

gcagcaggga cggctgacac 20

<210> SEQ ID NO 265
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 265

agaagcaacc gggcagcagg 20

<210> SEQ ID NO 266
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 266

cccaaaagag aagcaaccgg 20

<210> SEQ ID NO 267
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 267

accccgcccc caaaagagaa 20

<210> SEQ ID NO 268
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 268

cttgctagac cccgccccca 20

<210> SEQ ID NO 269
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 269

cacctgctct tgctagaccc 20

<210> SEQ ID NO 270

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 270

taaacccaca cctgctcttg 20

<210> SEQ ID NO 271
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 271

ctcctaaacc cacacctgct 20

<210> SEQ ID NO 272
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 272

acacacacct cctaaaccca 20

<210> SEQ ID NO 273
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 273

aaacaaaaac acacacctcc 20

<210> SEQ ID NO 274
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 274

ggtgggaaaa acaaaaacac 20

<210> SEQ ID NO 275
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 275

ctgtgagagc aagtagtggg 20

<210> SEQ ID NO 276
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 276

agcgagtact gtgagagcaa 20

<210> SEQ ID NO 277
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 277

tcaccctcag cgagtactgt 20

<210> SEQ ID NO 278
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 278

tcaggtcttt tcttgttcac 20

<210> SEQ ID NO 279
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 279

aatctttatc aggtcttttc 20

<210> SEQ ID NO 280
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 280

ttctggttaa tctttatcag 20

<210> SEQ ID NO 281
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 281

ttgttttctt ctggttaatc 20

<210> SEQ ID NO 282
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 282

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ttccctcctt gttttcttct 20

<210> SEQ ID NO 283
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 283

gcggttgttt ccctccttgt 20

<210> SEQ ID NO 284
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 284

tacaggctgc ggttgtttcc 20

<210> SEQ ID NO 285
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 285

gagcttgcta caggctgcgg 20

<210> SEQ ID NO 286
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 286

gagttccaga gcttgctaca 20

<210> SEQ ID NO 287
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cgactcctga gttccagagc 20

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cccggcccct agcgcgcgac 20

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<223> OTHER INFORMATION: Synthetic oligonucleotide

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gcgcaggcac cgcaaccgca 20

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<211> LENGTH: 20
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 309

ctaacagaat aagaaaaaaa 20

<210> SEQ ID NO 310
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<212> TYPE: DNA
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<400> SEQUENCE: 310

gagcattaga tgagtgcttt 20

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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 311

tgcattccta agcaatgtgt 20

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<400> SEQUENCE: 312

tctaggcctt cacattaatt 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
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<400> SEQUENCE: 313

cctgtctatg cctaggtgaa 20

<210> SEQ ID NO 314
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 314

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<400> SEQUENCE: 315

gaggagaaga acataaacgc 20

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<212> TYPE: DNA
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taccacaagt ctggagccat 20

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<400> SEQUENCE: 317

gatactggat tgttgaaact 20

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tagtatgact ggagatttgg 20

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atcaaaaccc caaatgattt 20

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<400> SEQUENCE: 321

tcgacatcac tgcattccaa 20

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<212> TYPE: DNA
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<400> SEQUENCE: 322

caacagctgg agatggcggt 20

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<400> SEQUENCE: 323

atttgccact taaagcaatc 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 324

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<400> SEQUENCE: 325

caagaaaagt tatttctcca 20

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gaaggatttc tccatttaga 20

<210> SEQ ID NO 327

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<211> LENGTH: 20
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1.-**41**. (canceled)

42. A compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a C9ORF72 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar, a sugar surrogate, and a modified internucleoside linkage.

43. The compound of claim **42**, wherein the C9ORF72 nucleic acid is any of SEQ ID NO: 1, SEQ ID NO: 2, and/or SEQ ID NO: 3.

44. A compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12 consecutive nucleobases of any of the nucleobase sequences of SEQ ID Nos: 30-369.

45. A compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases 100% complementary to an equal length portion of nucleobases

(i) 1,446-1,479 of SEQ ID NO: 2;
(ii) 2,209-2,238 of SEQ ID NO: 2;
(iii) 7,870-7,949 of SEQ ID NO: 2;
(iv) 7,990-8,072 of SEQ ID NO: 2;
(v) 8,080-8,129 of SEQ ID NO: 2;
(vi) 8,200-8,258 of SEQ ID NO: 2;

(vii) 13,357-13,409 of SEQ ID NO: 2;
(viii) 24,306-24,340 of SEQ ID NO: 2;
(ix) 26,630-26,649 of SEQ ID NO: 2; or
(x) 27,037-27,075 of SEQ ID NO: 2.

46. The compound of claim **45**, wherein:
(i) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 288, 340-343, 346, 348, 349, 352, 354-356, 358-361, and 365-368;
(ii) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 206-208;
(iii) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 33-37 and 321-323;
(iv) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 40-47, 324, and 325;
(v) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 50, 51, 326, and 327;
(vi) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 56, 57, 58, 330, and 331;
(vii) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 72-76;
(viii) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 130-133;
(ix) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 140-142; or
(x) the nucleobase sequence of the modified oligonucleotide comprises at least 12 contiguous nucleobases of SEQ ID Nos: 164-166.

47. The compound of claim **42**, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

48. The compound of claim **44**, wherein the nucleobase sequence of the modified oligonucleotide is:
a) at least 90% complementary to an equal length portion of SEQ ID NO: 2; or
b) 100% complementary to an equal length portion of SEQ ID NO: 2.

49. The compound of claim **42**, wherein the modified oligonucleotide is a single-stranded modified oligonucleotide.

50. The compound of claim **49**, wherein the single-stranded modified oligonucleotide is a gapmer.

51. The compound of claim **42**, wherein:
a) at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, optionally wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage; or
b) each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, optionally wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

52. The compound of claim **42**, wherein at least one nucleobase of the modified oligonucleotide is a modified nucleobase, optionally wherein the modified nucleobase is a 5-methylcytosine.

53. The compound of claim **42**, wherein:
a) at least one nucleoside of the modified oligonucleotide comprises a modified sugar;
or
b) each nucleoside of the modified oligonucleotide comprises a modified sugar.

54. The compound of claim **53**, wherein the modified sugar is a bicyclic sugar.

55. The compound of claim **54**, wherein the bicyclic sugar comprises a chemical bridge between the 4' and 2' positions of the sugar, wherein the chemical bridge is selected from: 4'-CH(R)—O-2' and 4'-$(CH_2)_2$—O-2', wherein R is H, C_1-C_6 alkyl, or C_1-C_6 alkoxy, optionally wherein the chemical bridge is 4'-CH(R)—O-2' and wherein R is:
a) methyl;
b) H; or
c) —CH_2—O—CH_3.

56. The compound of claim **53**, wherein at least one modified sugar comprises a 2'-O-methoxyethyl group or a 2'-O-methyl group.

57. The compound of claim **42**, wherein at least one nucleoside of the oligonucleotide comprises a sugar surrogate, optionally wherein the sugar surrogate is a morpholino or a peptide nucleic acid.

58. The compound of claim **42**, wherein the modified oligonucleotide has a nucleobase sequence complementary to a region of C9ORF72 other than a hexanucleotide repeat expansion, wherein the hexanucleotide repeat expansion comprises any of GGGGCC, GGGGGG, GGGGCG, and GGGGGC.

59. The compound of claim **42**, wherein the modified oligonucleotide is a double-stranded modified oligonucleotide.

60. The compound of claim **42**, consisting of the modified oligonucleotide.

61. A conjugated antisense compound comprising the compound of claim **42**.

62. A double-stranded compound comprising the compound of claim **42**.

63. A conjugated antisense compound comprising the double-stranded compound of claim **62**.

64. A composition comprising a compound according to claim **42** and a pharmaceutically acceptable carrier or diluent.

65. The composition of claim **64**, wherein:
a) the pharmaceutically acceptable diluent is phosphate buffered saline (PBS); and/or
b) the oligonucleotide of the compound is a sodium salt.

66. A composition comprising a conjugated antisense compound according to claim **61** and a pharmaceutically acceptable carrier or diluent.

67. The composition of claim **66**, wherein:
a) the pharmaceutically acceptable diluent is phosphate buffered saline (PBS); and/or
b) the oligonucleotide of the compound is a sodium salt.

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