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(54) **MODULATION OF DYSTROPHIA MYOTONICA-PROTEIN KINASE (DMPK) EXPRESSION**

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(57) **ABSTRACT**

Provided herein are methods, compounds, and compositions for reducing expression of a DMPK mRNA and protein in an animal. Also provided herein are methods, compounds, and compositions for preferentially reducing CUGexp DMPK RNA, reducing myotonia or reducing spliceopathy in an animal. Such methods, compounds, and compositions are useful to treat, prevent, delay, or ameliorate type 1 myotonic dystrophy, or a symptom thereof.

MODULATION OF DYSTROPHIA MYOTONICA-PROTEIN KINASE (DMPK) 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 BIOL0134USL2SEQ.txt created Jul. 19, 2011, which is approximately 216 Mb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are methods, compounds, and compositions for reducing expression of DMPK mRNA and protein in an animal. Also, provided herein are methods, compounds, and compositions comprising a DMPK inhibitor for preferentially reducing CUGexp DMPK RNA, reducing myotonia, or reducing spliceopathy in an animal. Such methods, compounds, and compositions are useful, for example, to treat, prevent, or ameliorate type 1 myotonic dystrophy (DM1) in an animal.

BACKGROUND

[0003] Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy in adults with an estimated frequency of 1 in 7,500 (Harper P S., Myotonic Dystrophy. London: W.B. Saunders Company; 2001). DM1 is an autosomal dominant disorder caused by expansion of a non-coding CTG repeat in DMPK1. DMPK1 is a gene encoding a cytosolic serine/threonine kinase (Brook J D, et al., *Cell.,* 1992, 68(4):799-808). The physiologic functions and substrates of this kinase have not been fully determined. The expanded CTG repeat is located in the 3' untranslated region (UTR) of DMPK1. This mutation leads to RNA dominance, a process in which expression of RNA containing an expanded CUG repeat (CUGexp) induces cell dysfunction (Osborne R J and Thornton C A., *Human Molecular Genetics.,* 2006, 15(2): R162-R169).

[0004] The DMPK gene normally has 5-37 CTG repeats in the 3' untranslated region. In myotonic dystrophy type I, this number is significantly expanded and is, for example, in the range of 50 to greater than 3,500 (Harper, Myotonic Dystrophy (Saunders, London, ed. 3, 2001); Arum. Rev. Neurosci. 29: 259, 2006; EMBO J. 19: 4439, 2000; Curr Opin Neurol. 20: 572, 2007).

[0005] The CUGexp tract interacts with RNA binding proteins including muscleblind-like (MBNL) protein, a splicing factor, and causes the mutant transcript to be retained in nuclear foci. The toxicity of this RNA stems from sequestration of RNA binding proteins and activation of signaling pathways. Studies in animal models have shown that phenotypes of DM1 can be reversed if toxicity of CUGexp RNA is reduced (Wheeler T M, et al., *Science.,* 2009, 325(5938):336-339; Mulders S A, et al., *Proc Natl Acad Sci USA.,* 2009, 106(33):13915-13920).

[0006] In DM1, skeletal muscle is the most severely affected tissue, but the disease also has important effects on cardiac and smooth muscle, ocular lens, and brain. The cranial, distal limb, and diaphragm muscles are preferentially affected. Manual dexterity is compromised early, which causes several decades of severe disability. The median age at death is 55 years, usually from respiratory failure (de Die-Smulders C E, et al., *Brain.,* 1998, 121(Pt 8):1557-1563).

[0007] Antisense technology is emerging as an effective means for modulating expression of certain gene products and may therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications for the modulation of DMPK1. Intramuscular injection of fully modified oligonucleotides targeting with the CAG-repeat were shown in mice to block formation of CUGexp-MBNL1 complexes, disperse nuclear foci of CUGexp transcripts, enhance the nucleocytoplasmic transport and translation of CUGexp transcripts, release MBNL proteins to the nucleoplasm, normalize alternative splicing of MBNL-dependent exons, and eliminate myotonia in CUGexp-expressing transgenic mice (Wheeler T M, et al., *Science.,* 2009, 325(5938): 336-339; WO2008/036406).

[0008] Presently there is no treatment that can modify the course of DM1. The burden of disease, therefore, is significant. It is, therefore, an object herein to provide compounds, compositions, and methods for treating DM1

SUMMARY

[0009] Provided herein are methods, compounds, and compositions for inhibiting expression of DMPK and treating, preventing, delaying or ameliorating a DMPK related disease and or a symptom thereof. In certain embodiments, the compounds and compositions inhibit mutant DMPK or CUGexp DMPK.

[0010] Certain embodiments provide a method of reducing DMPK expression in an animal comprising administering to the animal a compound comprising a modified oligonucleotide as further described herein targeted to DMPK.

[0011] Certain embodiments provide a method of preferentially reducing CUGexp DMPK, reducing myotonia, or reducing spliceopathy in an animal comprising administering to the animal a compound comprising a modified oligonucleotide, as further described herein, targeted to CUGexp DMPK. CUGexp DMPK transcripts are believed to be particularly sensitive to antisense knockdown via nuclear ribonucleases, because of their longer residence time in the nucleus, and this sensitivity is thought to permit effective antisense inhibition of CUGexp DMPK transcripts in relevant tissues such as muscle despite the biodistribution barriers to tissue uptake of antisense oligonucleotides. Antisense mechanisms that do not elicit cleavage via nuclear ribonucleases, such as the CAG-repeat ASOs described in, for example, Wheeler T M, et al., Science., 2009, 325(5938):336-339 and WO2008/036406, do not provide the same therapeutic advantage.

[0012] Certain embodiments provide a method of treating an animal with type 1 myotonic dystrophy. In certain embodiments, the method includes administering to the animal a therapeutically effective amount of a compound comprising a modified oligonucleotide as further described herein targeted to DMPK. In certain embodiments, the method includes identifying an animal with type 1 myotonic dystrophy.

[0013] Certain embodiments provide a method of treating, preventing, delaying, or ameliorating symptoms and outcomes associated with development of DM1 including muscle stiffness, myotonia, disabling distal weakness, weakness in face and jaw muscles, difficulty in swallowing, drooping of the eyelids (ptosis), weakness of neck muscles, weakness in arm and leg muscles, persistent muscle pain, hypersomnia, muscle wasting, dysphagia, respiratory insuf-

ficiency, irregular heartbeat, heart muscle damage, apathy, insulin resistance, and cataracts. Certain embodiments provide a method of treating, preventing, delaying, or ameliorating symptoms and outcomes associated with development of DM1 in children, including, developmental delays, learning problems, language and speech issues, and personality development issues.

[0014] Certain embodiments provide a method of administering an antisense oligonucleotide to counteract RNA dominance by directing the cleavage of pathogenic transcripts.

[0015] In certain embodiments, the DMPK has a sequence as set forth in GenBank Accession No. NM_001081560.1 (incorporated herein as SEQ ID NO: 1). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NT_011109.15 truncated from nucleotides 18540696 to 18555106 (incorporated herein as SEQ ID NO: 2). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NT_039413.7 truncated from nucleotides 16666001 to 16681000 (incorporated herein as SEQ ID NO: 3). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NM_032418.1 (incorporated herein as SEQ ID NO: 4). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. AI007148.1 (incorporated herein as SEQ ID NO: 5). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. AI304033.1 (incorporated herein as SEQ ID NO: 6). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BC024150.1 (incorporated herein as SEQ ID NO: 7). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BC056615.1 (incorporated herein as SEQ ID NO: 8). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BC075715.1 (incorporated herein as SEQ ID NO: 793). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BU519245.1 (incorporated herein as SEQ ID NO: 794). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. CB247909.1 (incorporated herein as SEQ ID NO: 795). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. CX208906.1 (incorporated herein as SEQ ID NO: 796). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. CX732022.1 (incorporated herein as SEQ ID NO: 797). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. S60315.1 (incorporated herein as SEQ ID NO: 798). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. S60316.1 (incorporated herein as SEQ ID NO: 799). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NM_001081562.1 (incorporated herein as SEQ ID NO: 800). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NM_001100.3 (incorporated herein as SEQ ID NO: 801).

DETAILED DESCRIPTION

[0016] 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. Herein, the use of "or" 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.

[0017] 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 application, including, but not limited to, patents, patent applications, articles, books, and treatises, are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

DEFINITIONS

[0018] 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 can be used for chemical synthesis, and chemical analysis. Where permitted, all patents, applications, published applications and other publications, 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 incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

[0019] Unless otherwise indicated, the following terms have the following meanings:

[0020] "2'-O-methoxyethyl" (also 2'-MOE and 2'-O$(CH_2)_2$—OCH_3) refers to an O-methoxy-ethyl modification of the 2' position of a furanosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

[0021] "2'-O-methoxyethyl nucleotide" means a nucleotide comprising a 2'-O-methoxyethyl modified sugar moiety.

[0022] "5-methylcytosine" means a cytosine modified with a methyl group attached to position 5. A 5-methylcytosine is a modified nucleobase.

[0023] "About" means within ±7% of a value. For example, if it is stated, "the compound affected at least 70% inhibition of DMPK", it is implied that the DMPK levels are inhibited within a range of 63% and 77%.

[0024] "Active 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 DMPK is an active pharmaceutical agent.

[0025] "Active target region" or "target region" means a region to which one or more active antisense compounds is targeted. "Active antisense compounds" means antisense compounds that reduce target nucleic acid levels or protein levels.

[0026] "Administered concomitantly" refers to the co-administration of two 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 agents be administered in a single pharmaceutical composition, in the same dosage form, or by the same route of administration. The effects of both 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.

[0027] "Administering" means providing an agent to an animal, and includes, but is not limited to, administering by a medical professional and self-administering.

[0028] "Agent" means an active substance that can provide a therapeutic benefit when administered to an animal. "First Agent" means a therapeutic compound of the invention. For example, a first agent can be an antisense oligonucleotide targeting DMPK. "Second agent" means a second therapeutic compound of the invention (e.g. a second antisense oligonucleotide targeting DMPK) and/or a non-DMPK therapeutic compound.

[0029] "Amelioration" refers to a lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. The severity of indicators can be determined by subjective or objective measures, which are known to those skilled in the art.

[0030] "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.

[0031] "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.

[0032] "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, snoRNAs, miRNAs, and satellite repeats.

[0033] "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.

[0034] "Antisense oligonucleotide" means a single-stranded oligonucleotide having a nucleobase sequence that permits hybridization to a corresponding region or segment of a target nucleic acid.

[0035] "Bicyclic sugar" means a furanosyl ring modified by the bridging of two non-geminal carbon ring atoms. A bicyclic sugar is a modified sugar.

[0036] "Bicyclic nucleic acid" or "BNA" refers to a nucleoside or nucleotide wherein the furanose portion of the nucleoside or nucleotide includes a bridge connecting two carbon atoms on the furanose ring, thereby forming a bicyclic ring system.

[0037] "Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

[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 nucleotides is chemically distinct from a region having nucleotides 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 agents to an individual. The two or more agents can be in a single pharmaceutical composition, or can be in separate pharmaceutical compositions. Each of the two or more agents can 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] "CUGexp DMPK" means mutant DMPK RNA containing an expanded CUG repeat (CUGexp). The wild-type DMPK gene has 5-37 CTG repeats in the 3' untranslated region. In a "CUGexp DMPK" (such as in a myotonic dystrophy type I patient) this number is significantly expanded and is, for example, in the range of 50 to greater than 3,500 (Harper, Myotonic Dystrophy (Saunders, London, ed. 3, 2001); Annu. Rev. Neurosci. 29: 259, 2006; EMBO J. 19: 4439, 2000; Curr Opin Neurol. 20: 572, 2007).

[0044] "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 can be a liquid, e.g. saline solution.

[0045] "DMPK" means any nucleic acid or protein of DMPK. DMPK can be a mutant DMPK including CUGexp DMPK nucleic acid.

[0046] "DMPK expression" means the level of mRNA transcribed from the gene encoding DMPK or the level of protein translated from the mRNA. DMPK expression can be determined by art known methods such as a Northern or Western blot.

[0047] "DMPK nucleic acid" means any nucleic acid encoding DMPK. For example, in certain embodiments, a DMPK nucleic acid includes a DNA sequence encoding DMPK, an RNA sequence transcribed from DNA encoding DMPK (including genomic DNA comprising introns and exons), and an mRNA or pre-mRNA sequence encoding DMPK. "DMPK mRNA" means an mRNA encoding a DMPK protein.

[0048] "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 can 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 can 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 can be stated as the amount of pharmaceutical agent per hour, day, week, or month.

[0049] "Effective amount" or "therapeutically effective amount" means the amount of active pharmaceutical agent sufficient to effectuate a desired physiological outcome in an individual in need of the agent. The effective amount can 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.

[0050] "Fully complementary" or "100% complementary" means each nucleobase of a nucleobase sequence of a first nucleic acid has a complementary nucleobase in a second nucleobase sequence of 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.

[0051] "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 can be referred to as a "gap segment" and the external regions can be referred to as "wing segments."

[0052] "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 one to six nucleosides.

[0053] "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.

[0054] "Identifying an animal with type 1 myotonic dystrophy" means identifying an animal having been diagnosed with a type 1 myotonic dystrophy, disorder or condition or identifying an animal predisposed to develop a type 1 myotonic dystrophy, disorder or condition. For example, individuals with a familial history can be predisposed to type 1 myotonic dystrophy, disorder or condition. Such identification can be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments.

[0055] "Immediately adjacent" means there are no intervening elements between the immediately adjacent elements.

[0056] "Individual" means a human or non-human animal selected for treatment or therapy.

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

[0058] "Linked nucleosides" means adjacent nucleosides which are bonded or linked together by an internucleoside linkage.

[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 at least one modified nucleotide.

[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] "Myotonia" means an abnormally slow relaxation of a muscle after voluntary contraction or electrical stimulation.

[0067] "Nuclear ribonuclease" means a ribonuclease found in the nucleus. Nuclear ribonucleases include, but are not limited to, RNase H including RNase H1 and RNase H2, the double stranded RNase drosha and other double stranded RNases.

[0068] "Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[0069] "Natural sugar moiety" means a sugar found in DNA (2'-H) or RNA (2'-OH).

[0070] "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). A nucleic acid can also comprise a combination of these elements in a single molecule.

[0071] "Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

[0072] "Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, or nucleobase modification.

[0073] "Nucleoside" means a nucleobase linked to a sugar.

[0074] "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.

[0075] "Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[0076] "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).

[0077] "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.

[0078] "Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

[0079] "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. Administration can be continuous, or chronic, or short or intermittent.

[0080] "Peptide" means a molecule formed by linking at least two amino acids by amide bonds. Peptide refers to polypeptides and proteins.

[0081] "Pharmaceutical composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition can comprise one or more active agents and a sterile aqueous solution.

[0082] "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.

[0083] "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 is a modified internucleoside linkage.

[0084] "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.

[0085] "Preferentially reducing CUG exp DMPK RNA" refers to a preferential reduction of RNA transcripts from a CUGexp DMPK allele relative to RNA transcripts from a normal DMPK allele.

[0086] "Prevent" 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.

[0087] "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.

[0088] "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. For example, increased aminotransferase levels in serum can indicate liver toxicity or liver function abnormality. For example, increased bilirubin can indicate liver toxicity or liver function abnormality.

[0089] "Single-stranded oligonucleotide" means an oligonucleotide which is not hybridized to a complementary strand.

[0090] "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.

[0091] "Spliceopathy" means a change in the alternative splicing of one or more RNAs that leads to the expression of altered splice products in a particular tissue.

[0092] "Subcutaneous administration" means administration just below the skin.

[0093] "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.

[0094] "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.

[0095] "Target nucleic acid," "target RNA," and "target RNA transcript" all refer to a nucleic acid capable of being targeted by antisense compounds.

[0096] "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.

[0097] "3' target site" refers to the 3'-most nucleotide of a target segment.

[0098] "Therapeutically effective amount" means an amount of an agent that provides a therapeutic benefit to an individual.

[0099] "Treat" refers to administering a pharmaceutical composition to effect an alteration or improvement of a disease, disorder, or condition.

[0100] "Type 1 myotonic dystrophy" or "DM1" means an autosomal dominant disorder caused by expansion of a non-coding CTG repeat in DMPK. This mutation leads to RNA dominance, a process in which expression of RNA containing an expanded CUG repeat (CUGexp) induced cell dysfunction. The CUGexp tract interacts with RNA binding proteins and causes the mutant transcript to be retained in nuclear foci. The toxicity of this RNA stems from sequestration of RNA binding proteins and activation of signaling pathways.

[0101] "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

[0102] Certain embodiments provide methods, compounds, and compositions for inhibiting DMPK expression.

[0103] Certain embodiments provide a method of reducing DMPK expression in an animal comprising administering to the animal a compound comprising a modified oligonucleotide targeting DMPK.

[0104] Certain embodiments provide a method of preferentially reducing CUGexp DMPK RNA, reducing myotonia or reducing spliceopathy in an animal comprising administering to the animal a compound comprising a modified oligonucleotide targeted to DMPK, wherein the modified oligonucleotide preferentially reduces CUGexp DMPK RNA, reduces myotonia or reduces spliceopathy in the animal.

[0105] Certain embodiments provide a method of administering an antisense oligonucleotide to counteract RNA dominance by directing the cleavage of pathogenic transcripts.

[0106] Certain embodiments provide a method of reducing spliceopathy of Serca1. In certain embodiments, methods provided herein result in exon 22 inclusion. In certain embodiments, the corrective splicing occurs in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0107] Certain embodiments provide a method of reducing spliceopathy of m-Titin. In certain embodiments, methods provided herein result in exon 5 inclusion. In certain embodiments, the corrective splicing occurs in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0108] Certain embodiments provide a method of reducing spliceopathy of Clcn1. In certain embodiments, methods provided herein result in exon 7a inclusion. In certain embodiments, the corrective splicing occurs in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0109] Certain embodiments provide a method of reducing spliceopathy of Zasp. In certain embodiments, methods provided herein result in exon 11 inclusion. In certain embodiments, the corrective splicing occurs in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0110] Certain embodiments provide a method for treating an animal with type 1 myotonic dystrophy comprising: a) identifying said animal with type 1 myotonic dystrophy, and b) administering to said animal a therapeutically effective amount of a compound comprising a modified oligonucleotide targeted to DMPK. In certain embodiments, the therapeutically effective amount of the compound administered to the animal preferentially reduces CUGexp DMPK RNA, reduces myotonia or reduces spliceopathy in the animal.

[0111] Certain embodiments provide a method of achieving a preferential reduction of CUGexp DMPK RNA, including administering to the subject suspected of having type 1 myotonic dystrophy or having a CUGexp DMPK RNA a modified antisense oligonucleotide complementary to a non-repeat region of said CUGexp DMPK RNA. The modified antisense oligonucleotide, when bound to said CUGexp DMPK RNA, achieves a preferential reduction of the CUGexp DMPK RNA.

[0112] Certain embodiments provide a method of achieving a preferential reduction of CUGexp DMPK RNA, including selecting a subject having type 1 myotonic dystrophy or having a CUGexp DMPK RNA and administering to said subject a modified antisense oligonucleotide complementary to a non-repeat region of said CUGexp DMPK RNA. The modified antisense oligonucleotide, when bound to the CUGexp DMPK RNA, activates a ribonuclease or nuclear ribonuclease, thereby achieving a preferential reduction of the CUGexp DMPK RNA in the nucleus.

[0113] Certain embodiments provide a method of achieving a preferential reduction of CUGexp DMPK RNA, including selecting a subject having type 1 myotonic dystrophy or having a mutant or CUGexp DMPK RNA and systemically administering to said subject a modified antisense oligonucleotide complementary to a non-repeat region of said CUGexp DMPK RNA. The modified antisense oligonucleotide, when bound to the mutant or CUGexp DMPK RNA, achieves a preferential reduction of the mutant or CUGexp DMPK RNA.

[0114] Certain embodiments provide a method of reducing myotonia in a subject in need thereof. The method includes administering to the subject a modified antisense oligonucleotide complementary to a non-repeat region of a DMPK RNA, wherein the modified antisense oligonucleotide, when bound to the DMPK RNA, activates a ribonuclease or nuclear ribonuclease, thereby reducing myotonia. In certain embodiments, the subject has or is suspected of having type 1 myotonic dystrophy or having a mutant DMPK RNA or CUGexp DMPK RNA. In certain embodiments, the DMPK RNA is nuclear retained.

[0115] Certain embodiments provide a method of reducing spliceopathy in a subject in need thereof. The method includes administering to the subject a modified antisense oligonucleotide complementary to a non-repeat region of a DMPK RNA, wherein the modified antisense oligonucleotide, when bound to the DMPK RNA, activates a ribonuclease or nuclear ribonuclease, thereby reducing spliceopathy. In certain embodiments, the subject has or is suspected of having type 1 myotonic dystrophy or having a nuclear retained CUGexp DMPK RNA. In certain embodiments, the DMPK RNA is nuclear retained. In certain embodiments, the spliceopathy is MBNL dependent spliceopathy.

[0116] In certain embodiments, the modified antisense oligonucleotide of the methods is chimeric. In certain embodiments, the modified antisense oligonucleotide of the methods is a gapmer.

[0117] In certain embodiments of the methods provided herein, the administering is subcutaneous. In certain embodiments, the administering is intravenous.

[0118] In certain embodiments, the modified antisense oligonucleotide of the methods targets a non-coding sequence within the non-repeat region of a DMPK RNA. In certain embodiments, the oligonucleotide targets a coding region, an intron, a 5'UTR, or a 3'UTR of the mutant DMPK RNA.

[0119] In certain embodiments of the methods provided herein, the nuclear ribonuclease is RNase H1.

[0120] In certain embodiments of the methods, the DMPK RNA is reduced in muscle tissue. In certain embodiments, the mutant DMPK RNA CUGexp DMPK RNA is preferentially reduced.

[0121] In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NM_001081560.1 (incorporated herein as SEQ ID NO: 1). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NT_011109.15 truncated from nucleotides 18540696 to 18555106 (incorporated herein as SEQ ID NO: 2). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NT_039413.7 truncated from nucleotides 16666001 to 16681000 (incorporated herein as SEQ ID NO: 3). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NM_032418.1 (incorporated herein as SEQ ID NO: 4). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. AI007148.1 (incorporated herein as SEQ ID NO: 5). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. AI304033.1 (incorporated herein as SEQ ID NO: 6). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BC024150.1 (incorporated herein as SEQ ID NO: 7). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BC056615.1 (incorporated herein as SEQ ID NO: 8). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BC075715.1 (incorporated herein as SEQ ID NO: 793). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. BU519245.1 (incorporated herein as SEQ ID NO: 794). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. CB247909.1 (incorporated herein as SEQ ID NO: 795). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. CX208906.1 (incorporated herein as SEQ ID NO: 796). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. CX732022.1 (incorporated herein as SEQ ID NO: 797). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. S60315.1 (incorporated herein as SEQ ID NO: 798). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. S60316.1 (incorporated herein as SEQ ID NO: 799). In certain embodiments, the DMPK has the sequence as set forth in GenBank Accession No. NM_001081562.1 (incorporated herein as SEQ ID NO: 800). In certain embodiments, the DMPK has the sequence as

set forth in GenBank Accession No. NM_001100.3 (incorporated herein as SEQ ID NO: 801).

[0122] In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 8 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792. In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 9, at least 10, or at least 11, contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792.

[0123] In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 12 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792. In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 13, or at least 14, contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792.

[0124] In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 15 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792. In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 16, or at least 17, contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792.

[0125] In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 18 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792. In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 19 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792.

[0126] In certain embodiments, the modified oligonucleotides provided herein are targeted to any one of the following regions of SEQ ID NO: 1: 1178-1206, 2159-2182, 2174-2196, 2426-2447, 2450-2518, 2679-2704, and 2697-2725.

[0127] In certain embodiments, the modified oligonucleotides provided herein are targeted to any one of the following regions of SEQ ID NO 1: 178-223, 232-253, 279-299, 366-399, 519-541, 923-975, 1073-1105, 1171-1196, 1215-1246, 1263-1324, 1706-1734, 1743-1763, 1932-1979, 1981-2003, 2077-2108, and 2152-2173.

[0128] In certain embodiments, the modified oligonucleotides provided herein are targeted to any one of the following regions of SEQ ID NO: 2: 1251-1303, 1305-1326, 1352-1372, 3762-3795, 4170-4192, 5800-5852, 6124-6149, 6168-6199, 6216-6277, 11979-12007, 12016-12036, 12993-13042, 13044-13066, 13140-13171, and 13215-13236.

[0129] In certain embodiments, the animal is a human.

[0130] In certain embodiments, the compounds or compositions of the invention are designated as a first agent and the methods of the invention further comprise administering a second agent. In certain embodiments, the first agent and the second agent are co-administered. In certain embodiments the first agent and the second agent are co-administered sequentially or concomitantly.

[0131] In certain embodiments, administration comprises parenteral administration.

[0132] In certain embodiments, the compound is a single-stranded modified oligonucleotide. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 95% complementary to any one of SEQ ID NOs: 1-8 and 793-801 as measured over the entirety of said modified oligonucleotide. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is 100% complementary to any one of SEQ ID NOs: 1-8 and 793-801 as measured over the entirety of said modified oligonucleotide.

[0133] In certain embodiments, at least one internucleoside linkage of said modified oligonucleotide is a modified internucleoside linkage. In certain embodiments, each internucleoside linkage is a phosphorothioate internucleoside linkage.

[0134] In certain embodiments, at least one nucleoside of said modified oligonucleotide comprises a modified sugar. In certain embodiments, at least one modified sugar is a bicyclic sugar. In certain embodiments, at least one modified sugar comprises a 2'-O-methoxyethyl or a 4'-$(CH_2)_n$—O-2' bridge, wherein n is 1 or 2.

[0135] In certain embodiments, at least one nucleoside of said modified oligonucleotide comprises a modified nucleobase. In certain embodiments, the modified nucleobase is a 5-methylcytosine.

[0136] In certain embodiments, the modified oligonucleotide comprises: a) a gap segment consisting of linked deoxynucleosides; b) a 5' wing segment consisting of linked nucleosides; and c) a 3' wing segment consisting of linked nucleosides. The gap segment is positioned between the 5' wing segment and the 3' wing segment and each nucleoside of each wing segment comprises a modified sugar.

[0137] In certain embodiments, the modified oligonucleotide comprises: a) a gap segment consisting of ten linked deoxynucleosides; b) a 5' wing segment consisting of five linked nucleosides; and c) a 3' wing segment consisting of five linked nucleosides. The gap segment is positioned between the 5' wing segment and the 3' wing segment, each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, each internucleoside linkage of said modified oligonucleotide is a phosphorothioate linkage, and each cytosine in said modified oligonucleotide is a 5'-methylcytosine.

[0138] In certain embodiments, the modified oligonucleotide consists of 20 linked nucleosides.

[0139] Certain embodiments provide a method of preferentially reducing CUGexp DMPK RNA, reducing myotonia or reducing spliceopathy in an animal comprising administering to the animal a compound comprising a modified oligonucleotide having a gap segment consisting of ten linked deoxynucleosides, a 5' wing segment consisting of five linked nucleosides and a 3' wing segment consisting of five linked nucleosides. The gap segment is positioned between the 5' wing segment and the 3' wing segment, each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, each internucleoside linkage of said modified oligonucleotide is a phosphorothioate linkage, each cytosine in said modified oligonucleotide is a 5'-methylcytosine.

[0140] Certain embodiments provide the use of any compound as described herein in the manufacture of a medicament for use in any of the therapeutic methods described herein. For example, certain embodiments provide the use of a compound as described herein in the manufacture of a medicament for treating, ameliorating, or preventing type 1 myotonic dystrophy. Certain embodiments provide the use of a compound as described herein in the manufacture of a medicament for inhibiting expression of DMPK and treating, preventing, delaying or ameliorating a DMPK related disease and or a symptom thereof. Certain embodiments provide the use of a compound as described herein in the manufacture of

a medicament for reducing DMPK expression in an animal. Certain embodiments provide the use of a compound as described herein in the manufacture of a medicament for preferentially reducing CUGexp DMPK, reducing myotonia, or reducing spliceopathy in an animal. Certain embodiments provide the use of a compound as described herein in the manufacture of a medicament for treating an animal with type 1 myotonic dystrophy. Certain embodiments provide the use of a compound as described herein in the manufacture of a medicament for treating, preventing, delaying, or ameliorating symptoms and outcomes associated with development of DM1 including muscle stiffness, myotonia, disabling distal weakness, weakness in face and jaw muscles, difficulty in swallowing, drooping of the eyelids (ptosis), weakness of neck muscles, weakness in arm and leg muscles, persistent muscle pain, hypersomnia, muscle wasting, dysphagia, respiratory insufficiency, irregular heartbeat, heart muscle damage, apathy, insulin resistance, and cataracts. Certain embodiments provide the use of a compound as described herein in the manufacture of a medicament for counteracting RNA dominance by directing the cleavage of pathogenic transcripts.

[0141] Certain embodiments provide a kit for treating, preventing, or ameliorating type 1 myotonic dystrophy as described herein wherein the kit comprises: a) a compound as described herein; and optionally b) an additional agent or therapy as described herein. The kit can further include instructions or a label for using the kit to treat, prevent, or ameliorate type 1 myotonic dystrophy.

[0142] Certain embodiments provide any compound or composition as described herein, for use in any of the therapeutic methods described herein. For example, certain embodiments provide a compound or composition as described herein for inhibiting expression of DMPK and treating, preventing, delaying or ameliorating a DMPK related disease and or a symptom thereof. Certain embodiments provide a compound or composition as described herein for use in reducing DMPK expression in an animal. Certain embodiments provide a compound or composition as described herein for use in preferentially reducing CUGexp DMPK, reducing myotonia, or reducing spliceopathy in an animal. Certain embodiments provide a compound or composition as described herein for use in treating an animal with type 1 myotonic dystrophy. Certain embodiments provide a compound or composition as described herein for use in treating, preventing, delaying, or ameliorating symptoms and outcomes associated with development of DM1 including muscle stiffness, myotonia, disabling distal weakness, weakness in face and jaw muscles, difficulty in swallowing, drooping of the eyelids (ptosis), weakness of neck muscles, weakness in arm and leg muscles, persistent muscle pain, hypersomnia, muscle wasting, dysphagia, respiratory insufficiency, irregular heartbeat, heart muscle damage, apathy, insulin resistance, and cataracts. Certain embodiments provide a compound or composition as described herein for use in counteracting RNA dominance by directing the cleavage of pathogenic transcripts. Certain embodiments provide compounds comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-156, 160-770, and 774-792.

[0143] Other compounds which can be used in the methods described herein are also provided.

[0144] For example, certain embodiments provide compounds comprising a modified oligonucleotide consisting of 10 to 80, 12 to 50, 12 to 30, 15 to 30, 18 to 24, 19 to 22, or 20 linked nucleosides having 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, or at least 19, contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 41, 44, 76, 109, 153, 320, 321, 322, 325, 329, 335, and 657.

[0145] Certain embodiments provide compounds comprising a modified oligonucleotide consisting of 10 to 80, 12 to 50, 12 to 30, 15 to 30, 18 to 24, 19 to 22, or 20, linked nucleosides having 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, contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 15, 73, 77, 79, 83, 85, 130, 602, 648, 655, 674, and 680.

[0146] Certain embodiments provide compounds comprising a modified oligonucleotide consisting of 10 to 80, 12 to 50, 12 to 30, 15 to 30, 18 to 24, 19 to 22, or 20, linked nucleosides having a nucleobase sequence comprising a portion of 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, or at least 19, or more, contiguous nucleobases complementary to an equal length portion of nucleobases 664-683, 773-792, 926-945, 927-946, 928-947, 931-950, 935-954, 941-960, 2089-2108, 2163-2182, 2490-2509, 2499-2518, 2676-2695, 2685-2704, 2676-2695, 2688-2707, 2697-2716, 2764-2783, and 2770-2789 of SEQ ID NO: 1, wherein the nucleobase sequence is complementary to SEQ ID NO: 1.

[0147] Certain embodiments provide compounds comprising a modified oligonucleotide consisting of 10 to 80, 12 to 50, 12 to 30, 15 to 30, 18 to 24, 19 to 22, or 20, linked nucleosides having a nucleobase sequence comprising a portion of 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, or at least 19, or more, contiguous nucleobases complementary to an equal length portion of nucleobases 812-831, 3629-3648, 4447-4466, 4613-4632, 5803-5822, 5804-5823, 5805-5824, 5808-5827, 5818-5837, 6794-6813, 12463-12482, 13152-13171, and 13553-13572 of SEQ ID NO: 2, wherein the nucleobase sequence is complementary to SEQ ID NO: 2.

[0148] In certain embodiments, the modified oligonucleotide is a single-stranded oligonucleotide.

[0149] In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100%, complementary to any of SEQ ID NOs: 1-8 and 793-801.

[0150] In certain embodiments, at least one internucleoside linkage is a modified internucleoside linkage.

[0151] In certain embodiments, each internucleoside linkage is a phosphorothioate internucleoside linkage.

[0152] In certain embodiments, at least one nucleoside comprises a modified sugar.

[0153] In certain embodiments, at least one modified sugar is a bicyclic sugar.

[0154] In certain embodiments, at least one modified sugar comprises a 2'-O-methoxyethyl.

[0155] In certain embodiments, at least one nucleoside comprises a modified nucleobase.

[0156] In certain embodiments, the modified nucleobase is a 5-methylcytosine.

[0157] In certain embodiments, the modified oligonucleotide comprises:

[0158] a gap segment consisting of linked deoxynucleosides;

[0159] a 5' wing segment consisting of linked nucleosides; and

[0160] a 3' wing segment consisting of linked nucleosides;

[0161] wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

[0162] In certain embodiments, the modified oligonucleotide comprises:

[0163] a gap segment consisting of ten linked deoxynucleosides;

[0164] a 5' wing segment consisting of five linked nucleosides; and

[0165] a 3' wing segment consisting of five linked nucleosides;

[0166] wherein the gap segment is positioned 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.

[0167] In certain embodiments, the modified oligonucleotide consists of 14 linked nucleosides.

[0168] In certain embodiments, the modified oligonucleotide consists of 16 linked nucleosides.

[0169] In certain embodiments, the modified oligonucleotide consists of 20 linked nucleosides.

Antisense Compounds

[0170] Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, and siRNAs. An oligomeric compound can be "antisense" to a target nucleic acid, meaning that is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

[0171] 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.

[0172] In certain embodiments, an antisense compound targeted to DMPK as described herein is 10 to 30 nucleotides in length. In other words, the antisense compounds are in some embodiments from 10 to 30 linked nucleobases. In other embodiments, the antisense compound comprises a modified oligonucleotide consisting of 8 to 80, 10 to 80, 12 to 30, 12 to 50, 15 to 30, 18 to 24, 19 to 22, or 20 linked nucleobases. In certain such embodiments, the antisense compound comprises a modified oligonucleotide consisting of 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 nucleobases in length, or a range defined by any two of the above values. In certain embodiments, antisense compounds of any of these lengths contain 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, or at least 19, contiguous nucleobases of the nucleobase sequence of any of the exemplary antisense compounds described herein (e.g., at least 8 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792.

[0173] In certain embodiments, the antisense compound comprises a shortened or truncated modified oligonucleotide. The shortened or truncated modified oligonucleotide can have a single nucleoside deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated oligonucleotide can have two nucleosides deleted from the 5' end, or alternatively can have two subunits deleted from the 3' end. Alternatively, the deleted nucleosides can be dispersed throughout the modified oligonucleotide, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

[0174] When a single additional nucleoside is present in a lengthened oligonucleotide, the additional nucleoside can be located at the 5' or 3' end of the oligonucleotide. When two or more additional nucleosides are present, the added nucleosides can be adjacent to each other, for example, in an oligonucleotide having two nucleosides added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the oligonucleotide. Alternatively, the added nucleoside can be dispersed throughout the antisense compound, for example, in an oligonucleotide having one nucleoside added to the 5' end and one subunit added to the 3' end.

[0175] 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.

[0176] Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity in vivo.

[0177] 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

[0178] In certain embodiments, antisense compounds targeted to a DMPK nucleic acid have chemically modified subunits arranged in patterns, or motifs, to confer to the

antisense compounds properties such as enhanced the inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by in vivo nucleases.

[0179] 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 can optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

[0180] 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 can in some embodiments include β-D-ribonucleosides, β-D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides can include 2'-MOE, and 2'-O—CH_3, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides can include those having a 4'-$(CH_2)_n$—O-2' bridge, where n=1 or n=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 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 include, but are not limited to, for example 5-10-5, 4-8-4, 4-12-3, 4-12-4, 3-14-3, 2-13-5, 2-16-2, 1-18-1, 3-10-3, 2-10-2, 1-10-1, 2-8-2, 6-8-6, 5-8-5, 1-8-1, or 2-6-2.

[0181] In certain embodiments, the antisense compound as 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 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, or 5-13.

[0182] In certain embodiments, antisense compounds targeted to a DMPK nucleic acid possess a 5-10-5 gapmer motif.

[0183] In certain embodiments, an antisense compound targeted to a DMPK nucleic acid has a gap-widened motif.

[0184] In certain embodiments, antisense compounds of any of these gapmer or wingmer motifs contain 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, or at least 19, contiguous nucleobases of the nucleobase sequence of any of the exemplary antisense compounds described herein (e.g., at least 8 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

[0185] Nucleotide sequences that encode DMPK include, without limitation, the following sequences as set forth in GenBank Accession No. NM_001081560.1 (incorporated herein as SEQ ID NO: 1), GenBank Accession No. NT_011109.15 truncated from nucleotides 18540696 to 18555106 (incorporated herein as SEQ ID NO: 2), GenBank Accession No. NT_039413.7 truncated from nucleotides 16666001 to 16681000 (incorporated herein as SEQ ID NO: 3), GenBank Accession No. NM_032418.1 (incorporated herein as SEQ ID NO: 4), GenBank Accession No. AI007148.1 (incorporated herein as SEQ ID NO: 5), GenBank Accession No. AI304033.1 (incorporated herein as SEQ ID NO: 6), GenBank Accession No. BC024150.1 (incorporated herein as SEQ ID NO: 7), GenBank Accession No. BC056615.1 (incorporated herein as SEQ ID NO: 8), GenBank Accession No. BC075715.1 (incorporated herein as SEQ ID NO: 793), GenBank Accession No. BU519245.1 (incorporated herein as SEQ ID NO: 794), GenBank Accession No. CB247909.1 (incorporated herein as SEQ ID NO: 795), GenBank Accession No. CX208906.1 (incorporated herein as SEQ ID NO: 796), GenBank Accession No. CX732022.1 (incorporated herein as SEQ ID NO: 797), GenBank Accession No. S60315.1 (incorporated herein as SEQ ID NO: 798), GenBank Accession No. S60316.1 (incorporated herein as SEQ ID NO: 799), GenBank Accession No. NM_001081562.1 (incorporated herein as SEQ ID NO: 800), and GenBank Accession No. NM_001100.3 (incorporated herein as SEQ ID NO: 801). 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 can 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.

[0186] In certain embodiments, a target region is a structurally defined region of the target nucleic acid. For example, a target region can 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 DMPK 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 can 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 target region.

[0187] 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.

[0188] A target region can contain one or more target segments. Multiple target segments within a target region can be

overlapping. Alternatively, they can 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 preceding 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.

[0189] Suitable target segments can 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 can specifically exclude a certain structurally defined region such as the start codon or stop codon.

[0190] The determination of suitable target segments can include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm can be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that can hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

[0191] There can be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within an active target region. In certain embodiments, reductions in DMPK mRNA levels are indicative of inhibition of DMPK protein expression. Reductions in levels of a DMPK protein are also indicative of inhibition of target mRNA expression. Further, phenotypic changes, such as a reducing myotonia or reducing spliceopathy, can be indicative of inhibition of DMPK mRNA and/or protein expression.

Hybridization

[0192] In some embodiments, hybridization occurs between an antisense compound disclosed herein and a DMPK 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.

[0193] 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.

[0194] Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art (Sambrooke and Russell, Molecular Cloning: A Laboratory Manual, 3rd Ed., 2001). In certain embodiments, the antisense compounds provided herein are specifically hybridizable with a DMPK nucleic acid.

Complementarily

[0195] 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 DMPK nucleic acid).

[0196] An antisense compound can hybridize over one or more segments of a DMPK nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

[0197] 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 DMPK nucleic acid, a target region, target segment, or specified portion thereof. In certain embodiments, the antisense compounds are at least 70%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to a DMPK nucleic acid, a target region, target segment, or specified portion thereof, and contain 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, or at least 19, contiguous nucleobases of the nucleobase sequence of any of the exemplary antisense compounds described herein (e.g., at least 8 contiguous nucleobases of a nucleobase sequence recited in any one of SEQ ID NOs: 12-156, 160-770, and 774-792). Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods, and is measured over the entirety of the antisense compound.

[0198] 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 can 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).

[0199] 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, antisense compound can be fully complementary to a DMPK 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 can 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.

[0200] The location of a non-complementary nucleobase can be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases can be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they can be either 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.

[0201] In certain embodiments, antisense compounds that are, or are up to 10, 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 DMPK nucleic acid, or specified portion thereof.

[0202] In certain embodiments, antisense compounds that are, or are up to 10, 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 DMPK nucleic acid, or specified portion thereof.

[0203] 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 10 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 an 8, at least a 9, at least a 10, at least an 11, at least a 12, at least a 13, at least a 14, at least a 15, at least a 16, at least a 17, at least an 18, at least a 19, at least a 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

[0204] The antisense compounds provided herein can 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 can 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.

[0205] In certain embodiments, the antisense compounds, or portions thereof, are at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to one or more of the exemplary antisense compounds or SEQ ID NOs, or a portion thereof, disclosed herein.

Modifications

[0206] 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.

[0207] 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.

[0208] Chemically modified nucleosides can 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

[0209] 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.

[0210] 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.

[0211] In certain embodiments, antisense compounds targeted to a DMPK nucleic acid comprise one or more modified internucleoside linkages. 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

[0212] Antisense compounds of the invention 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).

[0213] 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)—$N(R_l)$—$(CH_2)_2$—$N(R_m)(R_n)$, where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[0214] Examples of bicyclic nucleic acids (BNAs) 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 BNA nucleosides wherein the bridge comprises one of the formulas: 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 PCT/US2008/068922 published as WO/2009/006478, published Jan. 8, 2009); 4'-CH_2—$N(OCH_3)$-2' (and analogs thereof see PCT/US2008/064591 published as 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 PCT/US2008/066154 published as WO 2008/154401, published on Dec. 8, 2008).

[0215] Further bicyclic nucleosides have been reported in published literature (see for example: Srivastava et al., *J. Am. Chem. Soc.,* 2007, 129(26) 8362-8379; Frieden et al., *Nucleic Acids Research,* 2003, 21, 6365-6372; Elayadi et al., *Curr. Opinion Invens. Drugs,* 2001, 2, 558-561; Braasch et al., *Chem. Biol.,* 2001, 8, 1-7; Orum et al., *Curr. Opinion Mol. Ther.,* 2001, 3, 239-243; Wahlestedt et al., *Proc. Natl. Acad. Sci. U.S.A.,* 2000, 97, 5633-5638; Singh et al., *Chem. Commun.,* 1998, 4, 455-456; Koshkin et al., *Tetrahedron,* 1998, 54, 3607-3630; Kumar et al., *Bioorg. Med. Chem. Lett.,* 1998, 8, 2219-2222; Singh et al., *J. Org. Chem.,* 1998, 63, 10035-10039; U.S. Pat. Nos. 7,399,845; 7,053,207; 7,034,133; 6,794,499; 6,770,748; 6,670,461; 6,525,191; 6,268,490; U.S. Patent Publication Nos.: US2008-0039618; US2007-0287831; US2004-0171570; U.S. patent application Ser. Nos. 12/129,154; 61/099,844; 61/097,787; 61/086,231; 61/056,564; 61/026,998; 61/026,995; 60/989,574; International applications WO 2007/134181; WO 2005/021570; WO 2004/106356; WO 94/14226; and PCT International Applications Nos.: PCT/US2008/068922; PCT/US2008/066154; and PCT/US2008/064591). 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).

[0216] In certain embodiments, bicyclic nucleosides comprise a bridge between the 4' and the 2' carbon atoms of the pentofuranosyl sugar moiety including without limitation, bridges comprising 1 or from 1 to 4 linked groups independently selected from —$[C(R_a)(R_b)]_n$—, —$C(R_a)$=$C(R_b)$—, —$C(R_a)$=N—, —$C(=NR_a)$—, —C(═O)—, —C(═S)—, —O—, —$Si(R_a)_2$—, —$S(=O)_x$—, and —$N(R_a)$—; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; 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, Oh, 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

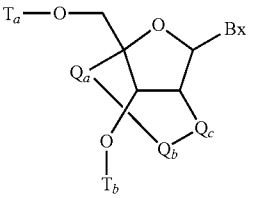
[0217] each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(═O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[0218] 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.

[0219] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-(CH_2)—O-2' 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).

[0220] In certain embodiments, bicyclic nucleosides include those having a 4' to 2' bridge wherein such bridges include without limitation, α-L-4'-(CH_2)—O-2', β-D-4'-CH_2—O-2', 4'-(CH_2)$_2$—O-2', 4'-CH_2—O—N(R)-2', 4'-CH_2—N(R)—O-2', 4'-$CH(CH_3)$—O-2', 4'-CH_2—S-2', 4'-CH_2—N(R)-2', 4'-CH_2—$CH(CH_3)$-2', and 4'-(CH_2)$_3$-2', wherein R is H, a protecting group or C_1-C_{12} alkyl.

[0221] In certain embodiments, bicyclic nucleosides have the formula:



wherein:

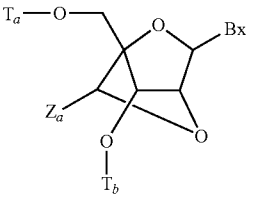
[0222] Bx is a heterocyclic base moiety;

[0223] -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;

[0224] R_c is C_1-C_{12} alkyl or an amino protecting group; and

[0225] 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.

[0226] In certain embodiments, bicyclic nucleosides have the formula:



wherein:

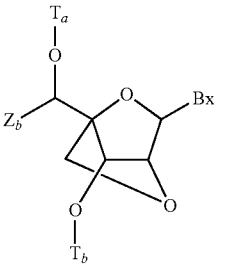
[0227] Bx is a heterocyclic base moiety;

[0228] 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;

[0229] 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 thiol.

[0230] 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.

[0231] In certain embodiments, bicyclic nucleosides have the formula:



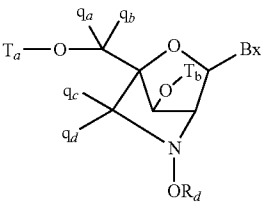
wherein:

[0232] Bx is a heterocyclic base moiety;

[0233] 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;

[0234] 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)—).

[0235] In certain embodiments, bicyclic nucleosides have the formula:



wherein:

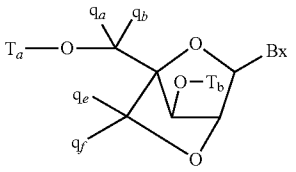
[0236] Bx is a heterocyclic base moiety;

[0237] 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;

[0238] 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;

[0239] 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;

[0240] In certain embodiments, bicyclic nucleosides have the formula:



wherein:

[0241] Bx is a heterocyclic base moiety;

[0242] 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;

[0243] 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;

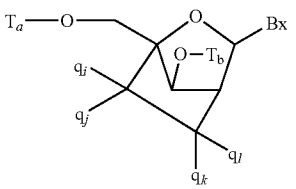
[0244] or q_e and q_f together are =C(q_g)(q_h);

[0245] q_g and q_h are each, independently, H, halogen, C_1-C_{12} alkyl or substituted C_1-C_{12} alkyl.

[0246] The synthesis and preparation of adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil bicyclic nucleosides having a 4'-CH_2—O-2' bridge, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin et al., *Tetrahedron,* 1998, 54, 3607-3630). The synthesis of bicyclic nucleosides has also been described in WO 98/39352 and WO 99/14226.

[0247] Analogs of various bicyclic nucleosides that have 4' to 2' bridging groups such as 4'-CH_2—O-2' and 4'-CH_2—S-2', have also been prepared (Kumar et al., *Bioorg. Med. Chem. Lett.,* 1998, 8, 2219-2222). Preparation of oligodeoxyribonucleotide duplexes comprising bicyclic nucleosides for use as substrates for nucleic acid polymerases has also been described (Wengel et al., WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel conformationally 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.

[0248] In certain embodiments, bicyclic nucleosides have the formula:



wherein:

[0249] Bx is a heterocyclic base moiety;

[0250] 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;

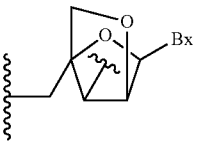
[0251] each q_i, q_j, q_k and q_l is, independently, H, halogen, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_1-C_{12} alkoxyl, substituted C_1-C_{12} alkoxyl, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, 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; and

[0252] 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.

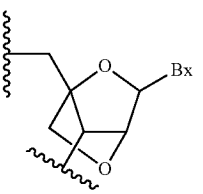
[0253] One carbocyclic bicyclic nucleoside having a 4'-$(CH_2)_3$-2' bridge and the alkenyl analog bridge 4'-CH=CH—CH_2-2' have been described (Frier et al., *Nucleic Acids Research,* 1997, 25(22), 4429-4443 and Albaek et al., *J. Org. Chem.,* 2006, 71, 7731-7740). The synthesis and preparation of carbocyclic 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).

[0254] 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, (F) methyl(methyleneoxy) (4'-CH(CH_3)—O-2') BNA (also referred to as constrained ethyl or cEt), (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, (J) propylene carbocyclic (4'-$(CH_2)_3$-2') BNA, and (K) vinyl BNA as depicted below.

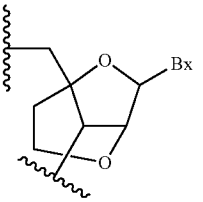
(A)



(B)



(C)



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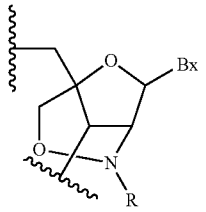
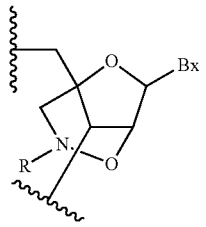
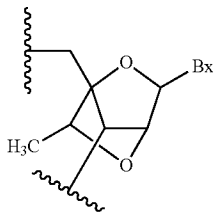
(D)



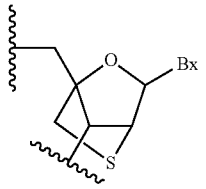
(E)



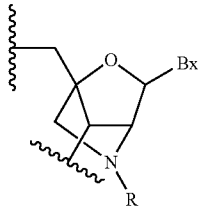
(F)



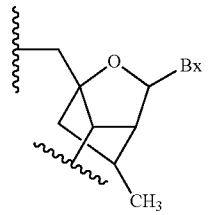
(G)



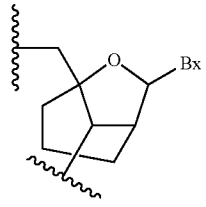
(H)



(I)



(J)



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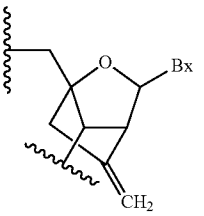
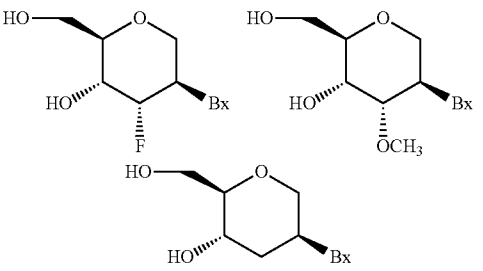
(K)

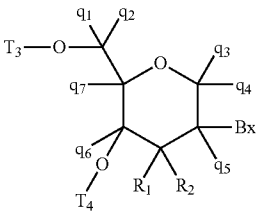


wherein Bx is the base moiety and R is, independently, H, a protecting group, C_1-C_6 alkyl or C_1-C_6 alkoxy.

[0255] In certain embodiments, nucleosides are modified by replacement of the ribosyl ring with a sugar surrogate. Such modification includes without limitation, replacement of the ribosyl ring with a surrogate ring system (sometimes referred to as DNA analogs) such as a morpholino ring, a cyclohexenyl ring, a cyclohexyl ring or a tetrahydropyranyl ring such as one having one of the formula:



[0256] In certain embodiments, sugar surrogates are selected having the formula:



wherein:

[0257] Bx is a heterocyclic base moiety;

[0258] T_3 and T_4 are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the oligomeric compound or one of T_3 and T_4 is an internucleoside linking group linking the tetrahydropyran nucleoside analog to an oligomeric compound or oligonucleotide and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group or a 5' or 3'-terminal group;

[0259] 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

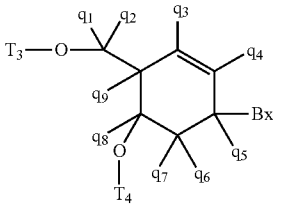
[0260] one of R_1 and R_2 is hydrogen and the other is selected from halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)$

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.

[0261] In certain embodiments, 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 are provided wherein one of R_1 and R_2 is F. 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 methoxyethoxy and R_2 is H.

[0262] Such sugar surrogates include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), altritol nucleic acid (ANA), and mannitol nucleic acid (MNA) (see Leumann, C. J., *Bioorg. & Med. Chem.,* 2002, 10, 841-854).

[0263] In certain embodiments, antisense compounds comprise one or more modified cyclohexenyl nucleosides, which is a nucleoside having a six-membered cyclohexenyl in place of the pentofuranosyl residue in naturally occurring nucleosides. Modified cyclohexenyl nucleosides include, but are not limited to those described in the art (see for example commonly owned, published PCT Application WO 2010/036696, published on Apr. 10, 2010, Robeyns et al., *J. Am. Chem. Soc.,* 2008, 130(6), 1979-1984; Horvath et al., *Tetrahedron Letters,* 2007, 48, 3621-3623; Nauwelaerts et al., *J. Am. Chem. Soc.,* 2007, 129(30), 9340-9348; Gu et al., *Nucleosides, Nucleotides & Nucleic Acids,* 2005, 24(5-7), 993-998; Nauwelaerts et al., *Nucleic Acids Research,* 2005, 33(8), 2452-2463; Robeyns et al., Acta Crystallographica, Section F: Structural Biology and Crystallization Communications, 2005, F61(6), 585-586; Gu et al., Tetrahedron, 2004, 60(9), 2111-2123; Gu et al., Oligonucleotides, 2003, 13(6), 479-489; Wang et al., *J. Org. Chem.,* 2003, 68, 4499-4505; Verbeure et al., Nucleic Acids Research, 2001, 29(24), 4941-4947; Wang et al., *J. Org. Chem.,* 2001, 66, 8478-82; Wang et al., *Nucleosides, Nucleotides & Nucleic Acids,* 2001, 20(4-7), 785-788; Wang et al., *J. Am. Chem.,* 2000, 122, 8595-8602; Published PCT application, WO 06/047842; and Published PCT Application WO 01/049687; the text of each is incorporated by reference herein, in their entirety). Certain modified cyclohexenyl nucleosides have the formula:



wherein:

[0264] Bx is a heterocyclic base moiety;

[0265] T_3 and T_4 are each, independently, an internucleoside linking group linking the cyclohexenyl nucleoside analog to an antisense compound or one of T_3 and T_4 is an internucleoside linking group linking the tetrahydropyran nucleoside analog to an antisense compound and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5'- or 3'-terminal group; and q_1, q_2, q_3, q_4, q_5, q_6, q_7, q_8 and q_9 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, substituted C_2-C_6 alkynyl or other sugar substituent group.

[0266] Many other bicyclic and tricyclic 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, Christian J., *Bioorg. & Med. Chem.,* 2002, 10, 841-854). Such ring systems can undergo various additional substitutions to enhance activity.

[0267] Methods for the preparations of modified sugars are well known to those skilled in the art. Some representative U.S. patents that teach the preparation of such modified sugars include without limitation, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,670,633; 5,700,920; 5,792,847 and 6,600,032 and International Application PCT/US2005/019219, filed Jun. 2, 2005 and published as WO 2005/121371 on Dec. 22, 2005, and each of which is herein incorporated by reference in its entirety.

[0268] 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.

[0269] In certain embodiments, antisense compounds targeted to a DMPK nucleic acid comprise one or more nucleotides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE. In certain embodiments, the 2'-MOE modified nucleotides are arranged in a gapmer motif.

Modified Nucleobases

[0270] Nucleobase (or base) modifications or substitutions are structurally distinguishable from, yet functionally interchangeable with, naturally occurring or synthetic unmodified nucleobases. Both natural and modified nucleobases are capable of participating in hydrogen bonding. Such nucleobase modifications can impart nuclease stability, binding affinity or some other beneficial biological property to antisense compounds. Modified nucleobases include synthetic and natural nucleobases such as, for example, 5-methylcytosine (5-me-C). Certain nucleobase substitutions, including 5-methylcytosine substitutions, are particularly useful for increasing the binding affinity of an antisense compound for a target nucleic acid. For example, 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., eds., Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278).

[0271] Additional unmodified nucleobases include 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (—C≡C—CH_3) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-aza-

guanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

[0272] Heterocyclic base moieties can also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Nucleobases that are particularly useful for increasing the binding affinity of antisense compounds include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2 aminopropyladenine, 5-propynyluracil and 5-propynylcytosine.

[0273] In certain embodiments, antisense compounds targeted to a DMPK nucleic acid comprise one or more modified nucleobases. In certain embodiments, gap-widened antisense oligonucleotides targeted to a DMPK nucleic acid comprise one or more modified nucleobases. In certain embodiments, the modified nucleobase is 5-methylcytosine. In certain embodiments, each cytosine is a 5-methylcytosine.

Compositions and Methods for Formulating Pharmaceutical Compositions

[0274] Antisense oligonucleotides can be admixed with pharmaceutically acceptable active or inert substance 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.

[0275] Antisense compound targeted to a DMPK 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 DMPK 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.

[0276] 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.

[0277] 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

[0278] Antisense compounds can 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.

[0279] 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

[0280] The effects of antisense compounds on the level, activity or expression of DMPK 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, Manassus, Va.; Zen-Bio, Inc., Research Triangle Park, N.C.; Clonetics Corporation, Walkersville, Md.) and cells 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, primary hepatocytes, A549 cells, GM04281 fibroblasts and LLC-MK2 cells.

In Vitro Testing of Antisense Oligonucleotides

[0281] Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

[0282] In general, cells are treated with antisense oligonucleotides when the cells reach approximately 60-80% confluence in culture.

[0283] 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.

[0284] Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE 2000® (Invitrogen, Carlsbad, Calif.). Antisense oligonucleotide is mixed with LIPOFECTAMINE 2000® 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.

[0285] Another reagent used to introduce antisense oligonucleotides into cultured cells includes Cytofectin® (Invitrogen, Carlsbad, Calif.). Antisense oligonucleotide is mixed with Cytofectin® in OPTI-MEM® 1 reduced serum medium (Invitrogen, Carlsbad, Calif.) to achieve the desired concen-

tration of antisense oligonucleotide and a Cytofectin® concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

[0286] Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation.

[0287] 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.

[0288] The concentration of antisense 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 LIPOFECTAMINE2000®, Lipofectin or Cytofectin. Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using electroporation.

RNA Isolation

[0289] 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

[0290] Inhibition of levels or expression of a DMPK 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

[0291] Quantitation of target RNA levels can 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.

[0292] 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.

[0293] 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 (Invitrogen, 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.

[0294] Probes and primers are designed to hybridize to a DMPK nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and can include the use of software such as PRIMER EXPRESS® Software (Applied Biosystems, Foster City, Calif.).

Analysis of Protein Levels

[0295] Antisense inhibition of DMPK nucleic acids can be assessed by measuring DMPK protein levels. Protein levels of DMPK 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.

In Vivo Testing of Antisense Compounds

[0296] Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of DMPK and produce phenotypic changes. Testing can be performed in normal animals, or in experimental disease models, for example, the HSA^{LR} mouse model of myotonic dystrophy (DM1).

[0297] The HSA^{LR} mouse model is an established model for DM1 (Mankodi, A. et al. Science. 289: 1769, 2000). The mice carry a human skeletal actin (hACTA1) transgene with 220 CTG repeats inserted in the 3' UTR of the gene. The hACTA1-CUG^{exp} transcript accumulates in nuclear foci in skeletal muscles and results in myotonia similar to that in human DM1 (Mankodi, A. et al. Mol. Cell 10: 35, 2002; Lin, X. et al. Hum. Mol. Genet. 15: 2087, 2006). Hence, it is expected that amelioration of DM1 symptoms in the HSA^{LR} mouse by antisense inhibition of the hACTA1 transgene would predict amelioration of similar symptoms in human patients by antisense inhibition of the DMPK transcript.

[0298] Expression of CUG^{exp} RNA in mice causes extensive remodeling of the muscle transcriptome, much of which is reproduced by ablation of MBNL1. Hence, it is expected that normalization of the transcriptome in HSA^{LR} mice would predict normalization of the human transcriptome in DM1 patients by antisense inhibition of the DMPK transcript.

[0299] For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as phosphate-buffered saline. Administration includes parenteral routes of administration. Following a period of treatment with antisense oligonucleotides, RNA is

isolated from tissue and changes in DMPK nucleic acid expression are measured. Changes in DMPK protein levels are also measured.

Splicing

[0300] Myotonic dystrophy (DM1) is caused by CTG repeat expansions in the 3' untranslated region of the DMPK gene (Brook, J. D. et al. Cell. 68: 799, 1992). This mutation leads to RNA dominance, a process in which expression of RNA containing an expanded CUG repeat (CUGexp) induces cell dysfunction (Osborne R J and Thornton C A., *Human Molecular Genetics.,* 2006, 15(2): R162-R169). Such CUGexp are retained in the nuclear foci of skeletal muscles (Davis, B. M. et al. Proc. Natl. Acad. Sci. U.S.A. 94:7388, 1997). The accumulation of CUGexp in the nuclear foci leads to the sequestration of poly(CUG)-binding proteins, such as, Muscleblind-like 1 (MBLN1) (Miller, J. W. et al. EMBO J. 19: 4439, 2000). MBLN1 is a splicing factor and regulates the splicing of genes such as Serca1, CIC-1, Titin, and Zasp. Therefore, sequestration of MBLN1 by CUGexp triggers misregulated alternative splicing of the exons of genes that MBLN1 normally controls (Lin, X. et al. Hum. Mol. Genet. 15: 2087, 2006). Correction of alternative splicing in an animal displaying such disregulation, such as, for example, in a DM1 patient and the HSALR mouse model, is a useful indicator for the efficacy of a treatment, including treatment with an antisense oligonucleotide.

Certain Biomarkers

[0301] DM1 severity in mouse models is determined, at least in part, by the level of CUG^{exp} transcript accumulation in the nucleus or nuclear foci. A useful physiological marker for DM1 severity is the development of high-frequency runs of involuntary action potentials (myotonia).

Certain Indications

[0302] In certain embodiments, provided herein are methods of treating an individual comprising administering one or more pharmaceutical compositions as described herein. In certain embodiments, the individual has type 1 myotonic dystrophy (DM1).

[0303] Accordingly, provided herein are methods for ameliorating a symptom associated with type 1 myotonic dystrophy in a subject in need thereof. In certain embodiments, provided is a method for reducing the rate of onset of a symptom associated with type 1 myotonic dystrophy. In certain embodiments, provided is a method for reducing the severity of a symptom associated with type 1 myotonic dystrophy. In certain embodiments, symptoms associated with DM1 include muscle stiffness, myotonia, disabling distal weakness, weakness in face and jaw muscles, difficulty in swallowing, drooping of the eyelids (ptosis), weakness of neck muscles, weakness in arm and leg muscles, persistent muscle pain, hypersomnia, muscle wasting, dysphagia, respiratory insufficiency, irregular heartbeat, heart muscle damage, apathy, insulin resistance, and cataracts. In children, the symptoms may also be developmental delays, learning problems, language and speech issues, and personality development issues.

[0304] In certain embodiments, the methods comprise administering to an individual in need thereof a therapeutically effective amount of a compound targeted to a DMPK nucleic acid.

[0305] In certain embodiments, administration of an antisense compound targeted to a DMPK nucleic acid results in reduction of DMPK expression by at least about 15%, by at least about 20%, by at least about 25%, by at least about 30%, by at least about 35%, by at least about 40%, by at least about 45%, by at least about 50%, by at least about 55%, by at least about 60%, by least about 65%, by least about 70%, by least about 75%, by least about 80%, by at least about 85%, by at least about 90%, by at least about 95% or by at least about 99%, or a range defined by any two of these values.

[0306] In certain embodiments, pharmaceutical compositions comprising an antisense compound targeted to DMPK are used for the preparation of a medicament for treating a patient suffering or susceptible to type 1 myotonic dystrophy.

[0307] In certain embodiments, the methods described herein include administering a compound comprising a modified oligonucleotide having a contiguous nucleobases portion as described herein of a sequence recited in SEQ ID NO: 12-156, 160-770, and 774-792.

Administration

[0308] In certain embodiments, the compounds and compositions as described herein are administered parenterally.

[0309] In certain embodiments, parenteral administration is by infusion. Infusion can be chronic or continuous or short or intermittent. In certain embodiments, infused pharmaceutical agents are delivered with a pump. In certain embodiments, parenteral administration is by injection (e.g., bolus injection). The injection can be delivered with a syringe.

[0310] Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g., intrathecal or intracerebroventricular administration. Administration can be continuous, or chronic, or short, or intermittent.

[0311] In certain embodiments, the administering is subcutaneous, intravenous, intracerebral, intracerebroventricular, intrathecal or another administration that results in a systemic effect of the oligonucleotide (systemic administration is characterized by a systemic effect, i.e., an effect in more than one tissue) or delivery to the CNS or to the CSF.

[0312] The duration of action as measured by inhibition of alpha 1 actin and reduction of myotonia in the HSA^{LR} mouse model of DM1 is prolonged in muscle tissue including quadriceps, gastrocnemius, and the tibialis anterior (see Examples, below). Subcutaneous injections of antisense oligonucleotide for 4 weeks results in inhibition of alpha 1 actin by at least 70% in quadriceps, gastrocnemius, and the tibialis anterior in HSA^{LR} mice for at least 11 weeks (77 days) after termination of dosing. Subcutaneous injections of antisense oligonucleotide for 4 weeks results in elimination of myotonia in quadriceps, gastrocnemius, and the tibialis anterior in HSA^{LR} mice for at least 11 weeks (77 days) after termination of dosing.

[0313] In certain embodiments, delivery of a compound of composition, as described herein, results in at least 70% down-regulation of a target mRNA and/or target protein for at least 77 days. In certain embodiments, delivery of a compound or composition, as described herein, results in 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% down-regulation of a target mRNA and/or target protein for at least 30 days, at least 35 days, at least 40 days, at least 45 days, at least 50 days, at least 55 days, at least 60 days, at least 65 days, at least 70 days, at least 75 days, at least 76 days, at least

77 days, at least 78 days, at least 79 days, at least 80 days, at least 85 days, at least 90 days, at least 95 days, at least 100 days, at least 105 days, at least 110 days, at least 115 days, at least 120 days, at least 1 year.

[0314] In certain embodiments, an antisense oligonucleotide is delivered by injection or infusion once every 77 days. In certain embodiments, an antisense oligonucleotide is delivered by injection or infusion once every month, every two months, every three months, every 6 months, twice a year or once a year.

Certain Combination Therapies

[0315] In certain embodiments, a first agent comprising the modified oligonucleotide of the invention is co-administered with one or more secondary agents. In certain embodiments, such second agents are designed to treat the same type 1 myotonic dystrophy as the first agent described herein. In certain embodiments, such second agents are designed to treat a different disease, disorder, or condition as the first agent described herein. In certain embodiments, such second agents are designed to treat an undesired side effect of one or more pharmaceutical compositions as described herein. In certain embodiments, second agents are co-administered with the first agent to treat an undesired effect of the first agent. In certain embodiments, second agents are co-administered with the first agent to produce a combinational effect. In certain embodiments, second agents are co-administered with the first agent to produce a synergistic effect.

[0316] In certain embodiments, a first agent and one or more second agents are administered at the same time. In certain embodiments, the first agent and one or more second agents are administered at different times. In certain embodiments, the first agent and one or more second agents are prepared together in a single pharmaceutical formulation. In certain embodiments, the first agent and one or more second agents are prepared separately.

EXAMPLES

Non-Limiting Disclosure and Incorporation by Reference

[0317] 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 Dystrophia Myotonica Protein Kinase (DMPK) in Human Skeletal Muscle Cells (hSKMC)

[0318] Antisense oligonucleotides targeted to a human DMPK nucleic acid were tested for their effect on DMPK RNA transcript in vitro. Cultured hSKM cells at a density of 20,000 cells per well were transfected using electroporation with 100 nM antisense oligonucleotide. After approximately 24 hours, RNA was isolated from the cells and DMPK RNA transcript levels were measured by quantitative real-time PCR with human primer probe set RTS3164 (forward sequence AGCCTGAGCCGGGAGATG, designated herein as SEQ ID NO: 9; reverse sequence GCGTAGTTGACTGGCGAAGTT, designated herein as SEQ ID NO: 10; probe sequence AGGCCATCCGCACGGACAACCX, designated herein as SEQ ID NO: 11). DMPK RNA transcript levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of hDMPK, relative to untreated control cells.

[0319] The antisense oligonucleotides in Tables 1 and 2 are 5-10-5 gapmers, where the gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises five 2'-MOE nucleosides. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. 'Target start site' indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted. 'Target stop site' indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted. All the antisense oligonucleotides listed in Table 1 target SEQ ID NO: 1 (GENBANK Accession No. NM_001081560.1). All the antisense oligonucleotides listed in Table 2 target SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_011109.15 truncated from nucleotides 18540696 to 18555106).

[0320] Several antisense oligonucleotides demonstrated significant inhibition of human DMPK mRNA levels under the conditions specified above.

TABLE 1

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
93	112	299476	CTGGCTGCATGTCTGCCTGT	81	12
277	296	299479	CCAGGAGAAGGTCGAGCAGG	57	13
737	756	299493	TCTATGGCCATGACAATCTC	57	14
773	792	299494	ATGTCCCTGTGCACGTAGCC	77	15
1194	1213	299501	ATGTGTCCGGAAGTCGCCTG	50	16
1628	1647	299511	CTCAGGCTCTGCCGGGTGAG	70	17
1855	1874	299517	GGCACTGGCCCACAGCCACG	78	18
2379	2398	299526	CCTGGCCGAAAGAAAGAAAT	31	19
2367	2386	444380	AAAGAAATGGTCTGTGATCC	56	20
2370	2389	444381	AAGAAAGAAATGGTCTGTGA	77	21
2376	2395	444382	GGCCGAAAGAAAGAAATGGT	61	22
2385	2404	444383	CCTCAGCCTGGCCGAAAGAA	57	23
2388	2407	444384	GGGCCTCAGCCTGGCCGAAA	65	24
2391	2410	444385	TCAGGGCCTCAGCCTGGCCG	61	25
2411	2430	444386	CTGCAGTTTGCCCATCCACG	68	26
2414	2433	444387	GGCCTGCAGTTTGCCCATCC	77	27
2417	2436	444388	CCAGGCCTGCAGTTTGCCCA	54	28
2423	2442	444389	GCCTTCCCAGGCCTGCAGTT	77	29
2426	2445	444390	GCTGCCTTCCCAGGCCTGCA	83	30

TABLE 1-continued

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
2429	2448	444391	CTTGCTGCCTTCCCAGGCCT	69	31
2435	2454	444392	GCCCGGCTTGCTGCCTTCCC	82	32
2438	2457	444393	ACGGCCCGGCTTGCTGCCTT	78	33
2441	2460	444394	CGGACGGCCCGGCTTGCTGC	57	34
2444	2463	444395	ACACGGACGGCCCGGCTTGC	73	35
2450	2469	444396	GATGGAACACGGACGGCCCG	80	36
2453	2472	444397	GAGGATGGAACACGGACGGC	86	37
2456	2475	444398	GTGGAGGATGGAACACGGAC	84	38
2481	2500	444399	GCGAACCAACGATAGGTGGG	80	39
2484	2503	444400	TTTGCGAACCAACGATAGGT	86	40
2490	2509	444401	TTGCACTTTGCGAACCAACG	89	41
2493	2512	444402	GCTTTGCACTTTGCGAACCA	89	42
2496	2515	444403	AAAGCTTTGCACTTTGCGAA	83	43
2499	2518	444404	AAGAAAGCTTTGCACTTTGC	91	44
2502	2521	444405	CACAAGAAAGCTTTGCACTT	70	45
2508	2527	444406	GTCATGCACAAGAAAGCTTT	34	46
2527	2546	444407	ACGCTCCCCAGAGCAGGGCG	39	47
2543	2562	444408	GCAGAGATCGCGCCAGACGC	85	48
2546	2565	444409	CAGGCAGAGATCGCGCCAGA	65	49
2549	2568	444410	AAGCAGGCAGAGATCGCGCC	84	50
2555	2574	444411	CCGAGTAAGCAGGCAGAGAT	58	51
2558	2577	444412	TTCCCGAGTAAGCAGGCAGA	70	52
2564	2583	444413	GCAAATTTCCCGAGTAAGCA	62	53
2567	2586	444414	AAAGCAAATTTCCCGAGTAA	53	54
2573	2592	444415	TTGGCAAAAGCAAATTTCCC	64	55
2576	2595	444416	GGTTTGGCAAAAGCAAATTT	23	56
2579	2598	444417	GCGGGTTTGGCAAAAGCAAA	70	57
2582	2601	444418	AAAGCGGGTTTGGCAAAAGC	43	58
2588	2607	444419	CCCGAAAAAGCGGGTTTGGC	71	59
2591	2610	444420	ATCCCCGAAAAAGCGGGTTT	53	60
2595	2614	444421	CGGGATCCCCGAAAAAGCGG	45	61
2598	2617	444422	GCGCGGGATCCCCGAAAAAG	48	62
2623	2642	444423	GAGAGCAGCGCAAGTGAGGA	77	63
2626	2645	444424	TCCGAGAGCAGCGCAAGTGA	62	64
2629	2648	444425	GGCTCCGAGAGCAGCGCAAG	79	65

TABLE 1-continued

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
2649	2668	444426	AAGCGGGCGGAGCCGGCTGG	20	66
2652	2671	444427	CCGAAGCGGGCGGAGCCGGC	0	67
2658	2677	444428	AAACCGCCGAAGCGGGCGGA	0	68
2661	2680	444429	TCCAAACCGCCGAAGCGGGC	45	69
2664	2683	444430	ATATCCAAACCGCCGAAGCG	31	70
2667	2686	444431	TAAATATCCAAACCGCCGAA	42	71
2670	2689	444432	CAATAAATATCCAAACCGCC	53	72
2676	2695	444433	CGAGGTCAATAAATATCCAA	63	73
2679	2698	444434	GGACGAGGTCAATAAATATC	83	74
2682	2701	444435	GGAGGACGAGGTCAATAAAT	82	75
2685	2704	444436	GTCGGAGGACGAGGTCAATA	86	76
2688	2707	444437	CGAGTCGGAGGACGAGGTCA	73	77
2694	2713	444438	TGTCAGCGAGTCGGAGGACG	79	78
2697	2716	444439	GCCTGTCAGCGAGTCGGAGG	83	79
2700	2719	444440	GTAGCCTGTCAGCGAGTCGG	94	80
2703	2722	444441	CCTGTAGCCTGTCAGCGAGT	90	81
2706	2725	444442	GGTCCTGTAGCCTGTCAGCG	90	82
2764	2783	444443	AAATACCGAGGAATGTCGGG	82	83
2767	2786	444444	AATAAATACCGAGGAATGTC	66	84
2770	2789	444445	GACAATAAATACCGAGGAAT	67	85
2093	2112	445546	CGGGGCCCCGGAGTCGAAGA	0	86
2097	2116	445547	CCAACGGGGCCCCGGAGTCG	38	87
2099	2118	445548	TTCCAACGGGGCCCCGGAGT	22	88
2102	2121	445549	GTCTTCCAACGGGGCCCCGG	50	89
2104	2123	445550	CAGTCTTCCAACGGGGCCCC	27	90
2106	2125	445551	CTCAGTCTTCCAACGGGGCC	57	91
2109	2128	445552	GCACTCAGTCTTCCAACGGG	69	92
2115	2134	445553	CCCCGGGCACTCAGTCTTCC	76	93
2117	2136	445554	TGCCCCGGGCACTCAGTCTT	59	94
2119	2138	445555	CGTGCCCCGGGCACTCAGTC	61	95
2123	2142	445556	GTGCCGTGCCCCGGGCACTC	26	96
2126	2145	445557	TCTGTGCCGTGCCCCGGGCA	50	97
2129	2148	445558	GCTTCTGTGCCGTGCCCCGG	57	98
2132	2151	445559	GCGGCTTCTGTGCCGTGCCC	27	99
2134	2153	445560	GCGCGGCTTCTGTGCCGTGC	0	100

TABLE 1-continued

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
2136	2155	445561	GGGCGCGGCTTCTGTGCCGT	8	101
2142	2161	445562	GGCGGTGGGCGCGGCTTCTG	62	102
2146	2165	445563	GGCAGGCGGTGGGCGCGGCT	49	103
2148	2167	445564	CTGGCAGGCGGTGGGCGCGG	51	104
2150	2169	445565	AACTGGCAGGCGGTGGGCGC	38	105
2153	2172	445566	GTGAACTGGCAGGCGGTGGG	64	106
2157	2176	445567	GGTTGTGAACTGGCAGGCGG	66	107
2159	2178	445568	GCGGTTGTGAACTGGCAGGC	85	108
2163	2182	445569	CGGAGCGGTTGTGAACTGGC	92	109
2167	2186	445570	CGCTCGGAGCGGTTGTGAAC	51	110
2171	2190	445571	CCCACGCTCGGAGCGGTTGT	74	111
2174	2193	445572	AGACCCACGCTCGGAGCGGT	80	112
2177	2196	445573	CGGAGACCCACGCTCGGAGC	83	113
2180	2199	445574	GGGCGGAGACCCACGCTCGG	62	114
2183	2202	445575	GCTGGGCGGAGACCCACGCT	11	115
2186	2205	445576	GGAGCTGGGCGGAGACCCAC	42	116
2188	2207	445577	CTGGAGCTGGGCGGAGACCC	17	117
2191	2210	445578	GGACTGGAGCTGGGCGGAGA	53	118
2193	2212	445579	CAGGACTGGAGCTGGGCGGA	46	119
2197	2216	445580	ATCACAGGACTGGAGCTGGG	66	120
2209	2228	445581	GGGCGGGCCCGGATCACAGG	85	121
2211	2230	445582	GGGGGCGGGCCCGGATCACA	96	122
179	198	445583	AGGCAGCACCATGGCCCCTC	88	123
235	254	445584	GGTCCAACACCAGCTGCTGG	84	124
418	437	445585	CGATCACCTTCAGAATCTCG	11	125
498	517	445586	CTTGTTCATGATCTTCATGG	0	126
565	584	445587	CCCCATTCACCAACACGTCC	83	127
583	602	445588	GCGTGATCCACCGCCGGTCC	59	128
639	658	445589	GTAATACTCCATGACCAGGT	86	129
664	683	445590	GCAGTGTCAGCAGGTCCCCG	83	130
744	763	445591	CACCGAGTCTATGGCCATGA	60	131
761	780	445592	ACGTAGCCAAGCCGGTGCAC	68	132
812	831	445593	ATGTGGCCACAGCGGTCCAG	56	133
1099	1118	445594	CTTCGTCCACCAGCGGCAGA	32	134
1104	1123	445595	GACCCCTTCGTCCACCAGCG	83	135

TABLE 1-continued

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1178	1197	445596	CCTGCTCCACCCCGGCCCAG	82	136
1187	1206	445597	CGGAAGTCGCCTGCTCCACC	81	137
1229	1248	445598	CGGAGACCATCCCAGTCGAG	67	138
1402	1421	445599	TGAGGGCCATGCAGGAGTAG	26	139
1443	1462	445600	CTCCAGTTCCATGGGTGTGG	80	140
1477	1496	445601	GCGCTTGCACGTGTGGCTCA	94	141
1526	1545	445602	GCCACTTCAGCTGTTTCATC	54	142
1562	1581	445603	GCCTCAGCCTCTGCCGCAGG	71	143
1576	1595	445604	GCAGCGTCACCTCGGCCTCA	31	144
1630	1649	445605	GGCTCAGGCTCTGCCGGGTG	86	145
1700	1719	445606	TTCCGAGCCTCTGCCTCGCG	73	146
1708	1727	445607	GGTCCCGGTTCCGAGCCTCT	76	147
1742	1761	445608	ATCCGCTCCTGCAACTGCCG	93	148
1750	1769	445609	GCAACTCCATCCGCTCCTGC	60	149
1812	1831	445610	AGGTGGATCCGTGGCCCGGG	48	150
2133	2152	445611	CGCGGCTTCTGTGCCGTGCC	24	151
2428	2447	445612	TTGCTGCCTTCCCAGGCCTG	80	152

TABLE 2

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
812	831	299471	TGCTCCCGACAAGCTCCAGA	95	153
876	895	299473	AGAACCTGCCCATTGCTGAA	68	154
2381	2400	299535	CACTGAGGGCCAGACATATG	68	155
3289	3308	299544	CTCTAGATTCAGATGCAGGT	88	156

[0321] The antisense oligonucleotides from Tables 1 and 2 were also tested in an assay with similar conditions as described above, and mRNA levels measured with the human primer probe RTS3162 (forward sequence CGGGCCGTC-CGTGTT, designated herein as SEQ ID NO: 157; reverse sequence CTTTGCACTTTGCGAACCAA, designated herein as SEQ ID NO: 158; probe sequence CATCCTC-CACGCACCCCCACCX, designated herein as SEQ ID NO: 159). The results are presented in Table 3. DMPK mRNA expression was also assessed by RTS3162 which targets the DMPK gene near the 3'UTR. The use of a second primer probe was employed to confirm that the expression of the entire DMPK gene had been inhibited

TABLE 3

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers measured using primer probe set RTS3162

ISIS No	% inhibition
299471	91
299473	65
299476	76
299479	53
299493	60
299494	66
299501	44
299511	39
299517	71
299526	39
299535	75
299544	84
444380	72
444381	82
444382	67
444383	63
444384	66
444385	66
444386	74
444387	85
444388	60
444389	81
444390	88
444391	79
444392	94
444393	88
444394	94
444395	96
444396	96
444397	95
444398	96
444399	95
444400	95
444401	95
444402	91
444403	84
444404	89
444405	71
444406	47
444407	42
444408	80
444409	56
444410	79
444411	66
444412	67
444413	55
444414	45
444415	57
444416	18
444417	64
444418	51
444419	66
444420	0
444421	46
444422	33
444423	74
444424	73
444425	78
444426	0
444427	0
444428	0
444429	75
444430	28
444431	58
444432	52
444433	60
444434	87
444435	76
444436	83
444437	71
444438	76

TABLE 3-continued

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers measured using primer probe set RTS3162

ISIS No	% inhibition
444439	73
444440	91
444441	87
444442	93
444443	77
444444	64
444445	67
445546	0
445547	59
445548	49
445549	77
445550	62
445551	74
445552	84
445553	70
445554	63
445555	75
445556	52
445557	78
445558	81
445559	58
445560	12
445561	42
445562	70
445563	76
445564	69
445565	60
445566	86
445567	84
445568	92
445569	93
445570	59
445571	84
445572	88
445573	84
445574	74
445575	26
445576	56
445577	38
445578	69
445579	70
445580	75
445581	85
445582	95
445583	88
445584	87
445585	34
445586	0
445587	82
445588	66
445589	87
445590	82
445591	68
445592	64
445593	54
445594	52
445595	77
445596	84
445597	78
445598	73
445599	29
445600	68
445601	92
445602	53
445603	70
445604	32
445605	61
445606	84
445607	80
445608	91
445609	68

TABLE 3-continued

Inhibition of human DMPK RNA transcript in hSKMC by 5-10-5 gapmers measured using primer probe set RTS3162

ISIS No	% inhibition
445610	63
445611	44
445612	91

Example 2

Design of Antisense Oligonucleotides Targeting CUG Repeats

[0322] Antisense oligonucleotides were designed targeting mRNA transcripts that contain multiple CUG repeats. The chemistry of these oligonucleotides as well as their sequence is shown in Table 4. The symbols designated to the sugar type are shown after the base in subscript and are as follows: b=2'-O—N-[2-(dimethylamino)ethyl]acetamido ribose; d=2'-deoxyribose; e=2'-β-methoxyethyl ribose; f=T-alpha-fluoro-T-deoxyribose; g=2'-O-2[2-(2-methoxyethoxy) ethoxy]ethyl ribose; h=3'-fluoro-HNA; k=(S)-cEt; l=LNA (Locked Nucleic Acids); n=2'-O-(N-methylacetamide) ribose; o=2'-O-dimethylaminooxyethyl (DMAOE) ribose; p=PNA; r=propylribose; and x=amino acid core. The heterocycle names are defined with standard symbols for adenine, cytosine, thymine and guanine, 'mC' for 5-methylcytosine, and 'K' for Lysine Side Chain. Linkers are shown after the sugar type in subscript and designated with the following symbols: g=PNA-glycine full; a=amino acid; and s=thioate ester.

TABLE 4

Design of antisense oligonucleotides targeting CUG repeats

ISIS No	Sequence	Chemistry	Backbone	SEQ ID NO
431896	$G_{ds}C_{ds}A_{ls}G_{ds}C_{ds}A_{ls}G_{ds}C_{ds}A_{ls}$ $G_{ds}C_{ds}A_{ls}G_{ds}C_{ds}A_{ls}G_{ds}C_{ds}A_{ls}G_{d}$	Deoxy and LNA units	Phosphorothioate	802
433804	$K_{xa}G_{pg}C_{pg}A_{pg}G_{pg}C_{pg}A_{pg}G_{pg}C_{pg}A_{pg}G_{pg}C_{pg}A_{pg}G_{pg}$ $C_{pg}A_{pg}G_{pg}C_{pg}A_{pg}G_{pg}K_{xa}K_{xa}K_{xa}K_{xa}K_{xa}K_{xa}K_{xa}K_{xa}$	PNA and Amino Acid Core units with a Carboxy-amide endcap	mixed	803
444745	$A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}$ $A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{e}$	Uniform MOE	Phosphorothioate	789
444746	$A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}$ $G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{e}$	Uniform MOE	Phosphorothioate	804
444747	$G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}$ $G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}$	Uniform MOE	Phosphorothioate	802
444748	$G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}$ $G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{es}G_{es}mC_{es}A_{e}$	Uniform MOE	Phosphorothioate	805
444750	$G_{ks}C_{ks}A_{ds}G_{ds}C_{ks}A_{ds}G_{ds}C_{ks}A_{ds}$ $G_{ds}C_{ks}A_{ds}G_{ds}C_{ks}A_{ds}G_{ds}C_{ks}A_{k}$	Deoxy and (S)-cEt units	Phosphorothioate	805
444752	$G_{ks}C_{ks}A_{es}G_{es}C_{ks}A_{es}G_{es}C_{ks}A_{es}$ $G_{es}C_{ks}A_{es}G_{es}C_{ks}A_{es}G_{es}C_{ks}A_{k}$	MOE and (S)-cEt units	Phosphorothioate	805
444754	$G_{es}mC_{es}A_{fs}G_{fs}C_{fs}A_{fs}G_{fs}C_{fs}A_{fs}$ $G_{fs}C_{fs}A_{fs}G_{fs}C_{fs}A_{fs}G_{fs}mC_{es}A_{es}$	MOE and 2'-alpha-flouro units	Phosphorothioate	805
444759	$G_{hs}mC_{hs}A_{hs}G_{hs}mC_{hs}A_{hs}G_{hs}mC_{hs}A_{hs}$ $G_{hs}mC_{hs}A_{hs}G_{hs}mC_{hs}A_{hs}G_{hs}mC_{hs}A_{h}$	Uniform 3'-fluoro-HNA	Phosphorothioate	805
444761	$G_{rs}mC_{rs}A_{rs}G_{rs}mC_{rs}A_{rs}G_{rs}mC_{rs}A_{rs}$ $G_{rs}mC_{rs}A_{rs}G_{rs}mC_{rs}A_{rs}G_{rs}mC_{rs}A_{r}$	Uniform 2'-O-propylribose	Phosphorothioate	805
444762	$G_{ns}mC_{ns}A_{ns}G_{ns}mC_{ns}A_{ns}G_{ns}mC_{ns}A_{ns}$ $G_{ns}mC_{ns}A_{ns}G_{ns}mC_{ns}A_{ns}G_{ns}mC_{ns}A_{n}$	Uniform 2'-O-(N-methylacetamide) ribose	Phosphorothioate	805
444763	$G_{os}mC_{es}A_{os}G_{os}mC_{es}A_{os}G_{os}mC_{es}A_{os}$ $G_{os}mC_{es}A_{os}G_{os}mC_{es}A_{os}G_{os}mC_{es}A_{o}$	MOE and 2'-O-dimethylaminooxyethyl (DMAOE) ribose units	Phosphorothioate	805
444764	$G_{gs}mC_{es}A_{es}G_{gs}mC_{es}A_{es}G_{gs}mC_{es}A_{es}$ $G_{gs}mC_{es}A_{es}G_{gs}mC_{es}A_{es}G_{gs}mC_{es}A_{es}G_{g}$	MOE and 2'-O-2[2-(2-methoxyethoxy)ethoxy] ethyl ribose units	Phosphorothioate	802
444765	$G_{bs}mC_{es}A_{es}G_{bs}mC_{es}A_{es}G_{bs}mC_{es}A_{es}$ $G_{bs}mC_{es}A_{es}G_{bs}mC_{es}A_{es}G_{bs}mC_{es}A_{es}G_{b}$	MOE and 2'-O-N-[2-(dimethylamino)ethyl] acetamido ribose units	Phosphorothioate	802

TABLE 4-continued

Design of antisense oligonucleotides targeting CUG repeats

ISIS No	Sequence	Chemistry	Backbone	SEQ ID NO
473810	$A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}mC_{ds}$ $A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}mC_{ds}A_k$	Deoxy and (S)-cEt units	Phosphorothioate	806
473811	$A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}$ $mC_{ds}A_{ks}G_{ds}mC_{ds}A_{ks}G_{ds}mC_{ds}A_k$	Deoxy and (S)-cEt units	Phosphorothioate	807

Example 3

Dose-Dependent Antisense Inhibition of Human DMPK in Human Skeletal Muscle Cells

[0323] Several of the antisense oligonucleotides exhibiting in vitro inhibition of DMPK in hSKMC (see Example 1) were tested at various doses. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 1,250 nM, 2,500 nM, 5,000 nM, 10,000 nM and 20,000 nM concentrations of each antisense oligonucleotide. After approximately 16 hours, RNA was isolated from the cells and DMPK mRNA transcript levels were measured by quantitative real-time PCR using primer probe set RTS3164, described hereinabove. DMPK mRNA transcript levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in Table 5 as percent inhibition of DMPK, relative to untreated control cells.

[0324] The tested antisense oligonucleotides demonstrated dose-dependent inhibition of DMPK mRNA levels under the conditions specified above.

TABLE 5

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No.	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
299471	34	65	87	91	94	1.60
299473	2	33	60	89	92	4.31
299476	15	17	49	81	91	4.89
299535	0	12	34	62	59	9.95
299535	20	33	47	67	80	5.11
299544	32	63	81	85	87	1.82
444397	10	30	58	85	82	4.51
444398	33	57	74	85	87	2.07
444400	52	46	63	82	88	1.76
444401	51	71	84	89	91	0.71
444402	53	79	83	87	84	<1.25
444404	48	68	77	86	90	0.95
444408	26	47	70	87	87	2.80
444410	22	47	67	83	87	3.12
444436	28	67	76	89	92	1.94
444440	70	77	83	89	85	<1.25
444441	33	55	81	87	86	1.99
444442	54	73	84	89	88	<1.25
445568	65	83	85	84	76	<1.25
445569	60	77	87	93	91	<1.25
445581	16	44	78	86	94	3.13
445582	0	7	26	96	99	5.60
445583	39	53	73	89	94	2.00
445584	20	26	61	81	93	4.02
445589	42	61	81	91	87	1.36
445601	49	79	87	93	94	0.66

TABLE 5-continued

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No.	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
445608	26	59	71	85	97	2.41
445612	46	59	72	88	93	1.51

[0325] The antisense oligonucleotides from Table 5 were also tested with primer probe set RTS3162, described hereinabove. The results are presented in Table 6. DMPK mRNA expression was also assessed by RTS3162 which targets the DMPK gene near the 3'UTR. The use of a second primer probe was employed to confirm that the expression of the entire DMPK gene had been inhibited.

TABLE 6

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No.	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
299471	40	72	86	91	93	1.17
299473	6	43	63	87	89	3.86
299476	3	21	48	74	86	5.58
299535	9	22	36	62	77	7.05
299535	6	19	49	68	70	6.70
299544	35	66	81	84	87	1.52
444397	88	90	95	97	96	<1.25
444398	91	97	97	97	98	<1.25
444400	72	87	93	96	96	<1.25
444401	86	92	97	98	97	<1.25
444402	83	91	94	95	95	<1.25
444404	49	69	81	90	93	0.92
444408	21	46	70	84	86	3.10
444410	35	55	77	89	91	2.02
444436	37	66	81	89	92	1.50
444440	66	79	89	92	89	<1.25
444441	40	62	85	89	89	1.40
444442	55	75	86	90	91	<1.25
445568	74	92	91	92	91	<1.25
445569	68	83	90	94	93	<1.25
445581	8	48	77	85	92	3.33
445582	15	22	44	97	99	4.29
445583	36	58	71	87	92	1.96
445584	25	43	66	86	94	3.05
445589	38	56	77	85	81	1.74
445601	55	76	84	93	93	<1.25
445608	22	56	72	86	94	2.66
445612	61	75	85	91	94	<1.25

Example 4

Dose-Dependent Antisense Inhibition of Human DMPK in Human Skeletal Muscle Cells

[0326] Several of the antisense oligonucleotides exhibiting in vitro inhibition of DMPK in hSKMC (see Example 3) were tested at various doses. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 1,250 nM, 2,500 nM, 5,000 nM, 10,000 nM and 20,000 nM concentrations of each antisense oligonucleotide. After approximately 16 hours, RNA was isolated from the cells and DMPK mRNA transcript levels were measured by quantitative real-time PCR using primer probe set RTS3164, described hereinabove. DMPK mRNA transcript levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in Table 7 as percent inhibition of DMPK, relative to untreated control cells.

[0327] The majority of the tested antisense oligonucleotides demonstrated dose-dependent inhibition of DMPK mRNA levels under the conditions specified above.

TABLE 7

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No.	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
299471	34	65	87	91	94	1.59
299473	2	33	60	89	92	4.31
299476	15	17	49	81	91	4.89
299535	0	12	34	62	59	9.95
299535	20	33	47	67	80	5.11
299544	32	63	81	85	87	1.82
444397	10	30	58	85	82	4.51
444398	33	57	74	85	87	2.07
444400	52	46	63	82	88	1.76
444401	51	71	84	89	91	<1.25
444402	53	79	83	87	84	<1.25
444404	48	68	77	86	90	0.95
444408	26	47	70	87	87	2.80
444410	22	47	67	83	87	3.12
444436	28	67	76	89	92	1.94
444440	66	77	83	89	85	<1.25
444441	33	55	81	87	86	1.99
444442	54	73	84	89	88	<1.25
445568	65	83	85	84	76	<1.25
445569	60	77	87	93	91	<1.25
445581	16	44	78	86	94	3.13
445582	0	7	26	96	99	5.62
445583	39	53	73	89	94	1.97
445584	20	26	61	81	93	4.20
445589	42	61	81	91	87	1.36
445601	49	79	87	93	94	0.66

TABLE 7-continued

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No.	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
445608	26	59	71	85	97	2.41
445612	46	59	72	88	93	1.51

Example 5

Dose-Dependent Antisense Inhibition of Human DMPK in Human Skeletal Muscle Cells

[0328] Several antisense oligonucleotides were designed to target human DMPK mRNA and were tested in hSKMC at various doses. Several other antisense oligonucleotides were designed to target human actin mRNA and were also tested in hSKMC at various doses. The newly designed gapmers are 2-10-2 MOE or 3-10-3 MOE gapmers. The 2-10-2 MOE gapmers are 14 nucleosides in length and where the gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises two 2'-MOE nucleosides. The 3-10-3 MOE gapmers are 16 nucleosides in length and where the gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises three 2'-MOE nucleosides. The internucleoside linkages throughout each gapmer are phosphorothioate (P═S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. 'Target start site' indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted. 'Target stop site' indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted. The antisense oligonucleotides listed in Table 8 target either the human DMPK genomic sequence, designated herein as SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_011109.15 truncated from nucleotides 18540696 to 18555106) or the human actin sequence, designated herein as SEQ ID NO: 801 (GENBANK Accession No. NM_001100.3).

[0329] Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 1,250 nM, 2,500 nM, 5,000 nM, 10,000 nM and 20,000 nM concentrations of each antisense oligonucleotide. After approximately 16 hours, RNA was isolated from the cells and DMPK mRNA transcript levels were measured by quantitative real-time PCR using primer probe set RTS3162, described hereinabove. DMPK mRNA transcript levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in Table 8 as percent inhibition of DMPK, relative to untreated control cells. The antisense oligonucleotides were also tested under similar conditions with RTS3164. The results are presented in Table 9.

[0330] Many of the tested antisense oligonucleotides demonstrated dose-dependent inhibition of DMPK mRNA levels under the conditions specified above.

TABLE 8

Dose-dependent antisense inhibition of human DMPK and human actin in hSKMC tested with primer probe set RTS3162

ISIS No	Sequence	Motif	Target SEQ ID NO	Start Site	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (nM)	SEQ ID NO
468787	CTCCCGACAAGCTCCA	3-10-3	2	814	28	47	51	84	88	3.27	808
468772	TCCCGACAAGCTCC	2-10-2	2	815	17	39	67	72	80	4.04	809
468795	GCTTGCACGTGTGGCT	3-10-3	2	10935	32	58	77	85	75	1.94	810

TABLE 8-continued

Dose-dependent antisense inhibition of human DMPK and human actin in hSKMC tested with primer probe set RTS3162

ISIS No	Sequence	Motif	Target SEQ ID NO	Start Site	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (nM)	SEQ ID NO
468780	CTTGCACGTGTGGC	2-10-2	2	10936	22	17	43	66	77	6.23	811
468793	GGTTGTGAACTGGCAG	3-10-3	2	13224	69	77	93	96	96	<1.25	812
468778	GTTGTGAACTGGCA	2-10-2	2	13225	60	69	89	95	97	<1.25	813
468794	GAGCGGTTGTGAACTG	3-10-3	2	13228	21	32	61	70	86	4.27	814
468779	AGCGGTTGTGAACT	2-10-2	2	13229	40	45	72	91	97	2.20	815
468796	GCTGCCTTCCCAGGCC	3-10-3	2	13493	73	79	91	96	95	<1.25	816
468781	CTGCCTTCCCAGGC	2-10-2	2	13494	36	53	66	86	90	2.28	817
468788	GCACTTTGCGAACCAA	3-10-3	2	13555	55	80	84	94	96	<1.25	818
468773	CACTTTGCGAACCA	2-10-2	2	13556	31	52	82	91	93	2.16	819
468789	GAAAGCTTTGCACTTT	3-10-3	2	13564	42	66	83	91	98	1.31	820
468774	AAAGCTTTGCACTT	2-10-2	2	13565	21	0	31	41	55	1.87	821
468790	CGGAGGACGAGGTCAA	3-10-3	2	13750	43	57	79	87	89	1.51	822
468775	GGAGGACGAGGTCA	2-10-2	2	13751	27	51	58	78	81	3.18	823
468791	AGCCTGTCAGCGAGTC	3-10-3	2	13765	49	63	85	62	95	1.04	824
468776	GCCTGTCAGCGAGT	2-10-2	2	13766	65	47	81	88	93	<1.25	825
468792	TCCTGTAGCCTGTCAG	3-10-3	2	13771	38	57	73	85	93	1.91	826
468777	CCTGTAGCCTGTCA	2-10-2	2	13772	15	58	66	85	92	2.99	827
468783	GAAGCGAGGCTTCACT	3-10-3	801	22	0	20	5	0	0	>20.00	828
468768	AAGCGAGGCTTCAC	2-10-2	801	23	25	22	5	17	0	>20.00	829
468784	ACCTGCCCGTCTGGCA	3-10-3	801	836	15	25	32	18	25	>20.00	830
468769	CCTGCCCGTCTGGC	2-10-2	801	837	32	11	11	20	32	>20.00	831
468782	GGTCAGCGATCCCAGG	3-10-3	801	1030	0	0	0	0	0	>20.00	832
468767	GTCAGCGATCCCAG	2-10-2	801	1031	15	0	11	0	0	>20.00	833
468785	ATTTTCTTCCACAGGG	3-10-3	801	1432	12	0	0	0	0	>20.00	834
468770	TTTTCTTCCACAGG	2-10-2	801	1433	36	2	0	0	28	>20.00	835
468786	GAATGACTTTAATGCT	3-10-3	801	1462	0	0	0	4	0	>20.00	836
468771	AATGACTTTAATGC	2-10-2	801	1463	8	16	0	5	0	>20.00	837

TABLE 9

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
468777	20	66	72	87	96	2.41
468776	68	48	86	90	96	<1.25
468794	18	23	58	65	86	4.97
468787	36	50	51	88	92	2.69

TABLE 9-continued

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
468772	12	47	69	80	86	3.57
468773	33	48	82	91	96	2.21
468774	21	0	30	42	59	1.60
468790	50	57	77	91	91	1.26

TABLE 9-continued

Dose-dependent antisense inhibition of human DMPK in hSKMC tested with primer probe set RTS3164

ISIS No	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
468780	23	22	55	73	85	4.69
468775	29	52	55	79	84	3.03
468782	9	0	0	0	0	>20.00
468786	2	0	0	0	0	>20.00
468785	15	0	1	0	5	>20.00
468788	57	74	76	94	96	<1.25
468791	45	66	88	61	97	1.10
468789	26	65	82	90	97	2.02
468781	28	46	59	82	84	3.08
468779	26	31	66	90	97	3.29
468784	7	23	26	7	18	>20.00
468783	0	16	8	0	0	>20.00
468792	26	49	73	84	92	2.72
468795	30	53	83	86	85	2.14
468793	49	66	90	96	95	0.93
468768	23	3	5	9	0	>20.00
468767	0	0	14	0	0	>20.00
468769	31	0	0	16	25	>20.00
468771	4	0	0	0	0	>20.00
468770	33	0	0	0	32	>20.00
468796	62	72	84	96	95	<1.25
468778	44	58	86	96	98	1.44

Example 6

Dose Response Studies with Antisense Oligonucleotides Targeting Human Dystrophia Myotonica-Protein Kinase (DMPK) in DM1 Fibroblast Cells

[0331] The mutant form of the DMPK mRNA, harboring large CUG repeats, are fully transcribed and polyadenylated, but remain trapped in the nucleus (Davis et al, 1997, *Proc. Natl. Acad. Sci. U.S.A.* 94, 7388-7393). These mutant nuclear-retained mRNAs are one of the most important pathological features of myotonic dystrophy 1 (DM1). Antisense inhibition of mutant DMPK mRNA in DM1 fibroblast cells was studied.

[0332] The DMPK gene normally has 5-37 CTG repeats in the 3' untranslated region. In myotonic dystrophy type I, this number is significantly expanded and may be in the range of 50 to greater than 3,500 (Harper, Myotonic Dystrophy (Saunders, London, ed. 3, 2001); Annu. Rev. Neurosci. 29: 259, 2006; EMBO J. 19: 4439, 2000; Curr Opin Neurol. 20: 572, 2007). DM1 fibroblast cells were plated at a density of 4,500 cells per well and transfected using Cytofectin reagent with 9.4 nM, 18.8 nM, 37.5 nM, 75.0 nM, 150.0 nM, and 300.0 nM concentrations of each antisense oligonucleotide. After approximately 16 hours, RNA was isolated from the cells and DMPK RNA transcript levels were measured by quantitative real-time PCR using primer probe set RTS3164, described hereinabove. DMPK RNA transcript levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in Table 10 as percent inhibition of DMPK, relative to untreated control cells.

[0333] An assay with similar conditions was also performed with primer probe set RTS3162, described hereinabove, which targets the 3'-end of the DMPK transcript. Results are presented in Table 11 as percent inhibition of DMPK, relative to untreated control cells.

[0334] The tested antisense oligonucleotides demonstrated dose-dependent inhibition of DMPK mRNA levels under the conditions specified above.

TABLE 10

Dose-dependent antisense inhibition of DMPK mRNA in DM1 fibroblast cells with RTS3164

ISIS No.	9.4 nM	18.8 nM	37.5 nM	75.0 nM	150.0 nM	300.0 nM	IC_{50} (nM)
299471	10	25	31	47	61	73	86.3
444401	8	27	41	60	67	74	64.3
444404	10	21	31	43	55	73	100.0
444436	7	17	36	64	68	70	72.3
445569	19	31	41	59	46	77	72.2

TABLE 11

Dose-dependent antisense inhibition of DMPK mRNA in DM1 fibroblast cells with RTS3162

ISIS No	9.4 nM	18.8 nM	37.5 nM	75.0 nM	150.0 nM	300.0 nM	IC_{50} (nM)
299471	7	25	29	46	48	69	115.3
444401	20	34	52	72	83	89	35.8
444404	5	20	28	42	54	77	98.8
444436	12	15	27	61	68	75	74.3
445569	5	25	33	53	50	76	89.6

Example 7

Antisense Inhibition of Human DMPK in Human Skeletal Muscle Cells (hSKMc)

[0335] Antisense oligonucleotides targeted to a human DMPK nucleic acid were tested for their effect on DMPK RNA transcript in vitro. Cultured hSKMc at a density of 20,000 cells per well were transfected using electroporation with 10,000 nM antisense oligonucleotide. After approximately 24 hours, RNA was isolated from the cells and DMPK transcript levels were measured by quantitative real-time PCR. DMPK RNA transcript levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of DMPK, relative to untreated control cells.

[0336] The antisense oligonucleotides in Tables 12 and 13 are 5-10-5 gapmers, where the gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises five 2'-MOE nucleosides. The internucleoside linkages throughout each gapmer are phosphorothioate (P═S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. 'Target start site' indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted in the human genomic gene sequence. 'Target stop site' indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted in the human genomic sequence. All the antisense oligonucleotides listed in Table 12 target SEQ ID NO: 1 (GENBANK Accession No. NM_001081560.1). All the antisense oligonucleotides listed in Table 13 target SEQ ID NO: 2 (the complement of GENBANK Accession No. NT_011109.15 truncated from nucleotides 18540696 to 18555106).

[0337] Several of the antisense oligonucleotides demonstrated significant inhibition of DMPK mRNA levels under the conditions specified above.

TABLE 12

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
124	143	502369	GCCTGGCAGCCCCTGTCCAG	16	160
125	144	502370	GGCCTGGCAGCCCCTGTCCA	58	161
126	145	502371	GGGCCTGGCAGCCCCTGTCC	62	162
169	188	502372	ATGGCCCCTCCCCGGGCCGG	41	163
170	189	502373	CATGGCCCCTCCCCGGGCCG	29	164
171	190	502374	CCATGGCCCCTCCCCGGGCC	34	165
172	191	502375	ACCATGGCCCCTCCCCGGGC	60	166
173	192	502376	CACCATGGCCCCTCCCCGGG	68	167
174	193	502377	GCACCATGGCCCCTCCCCGG	75	168
175	194	502378	AGCACCATGGCCCCTCCCCG	65	169
176	195	502379	CAGCACCATGGCCCCTCCCC	63	170
177	196	502380	GCAGCACCATGGCCCCTCCC	73	171
178	197	502381	GGCAGCACCATGGCCCCTCC	80	172
180	199	502382	CAGGCAGCACCATGGCCCCT	82	173
181	200	502383	ACAGGCAGCACCATGGCCCC	72	174
183	202	502384	GGACAGGCAGCACCATGGCC	70	175
184	203	502385	TGGACAGGCAGCACCATGGC	71	176
185	204	502386	TTGGACAGGCAGCACCATGG	73	177
186	205	502387	GTTGGACAGGCAGCACCATG	73	178
187	206	502388	TGTTGGACAGGCAGCACCAT	60	179
188	207	502389	ATGTTGGACAGGCAGCACCA	75	180
189	208	502390	CATGTTGGACAGGCAGCACC	81	181
190	209	502391	ACATGTTGGACAGGCAGCAC	67	182
191	210	502392	GACATGTTGGACAGGCAGCA	71	183
192	211	502393	TGACATGTTGGACAGGCAGC	81	184
193	212	502394	CTGACATGTTGGACAGGCAG	76	185
194	213	502395	GCTGACATGTTGGACAGGCA	70	186
195	214	502396	GGCTGACATGTTGGACAGGC	77	187
196	215	502397	CGGCTGACATGTTGGACAGG	74	188
197	216	502398	TCGGCTGACATGTTGGACAG	63	189
198	217	502399	CTCGGCTGACATGTTGGACA	80	190
199	218	502400	CCTCGGCTGACATGTTGGAC	71	191
200	219	502401	ACCTCGGCTGACATGTTGGA	64	192
201	220	502402	CACCTCGGCTGACATGTTGG	71	193
202	221	502403	GCACCTCGGCTGACATGTTG	77	194

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
203	222	502404	CGCACCTCGGCTGACATGTT	80	195
204	223	502405	CCGCACCTCGGCTGACATGT	80	196
205	224	502406	GCCGCACCTCGGCTGACATG	79	197
206	225	502407	AGCCGCACCTCGGCTGACAT	74	198
207	226	502408	CAGCCGCACCTCGGCTGACA	66	199
208	227	502409	TCAGCCGCACCTCGGCTGAC	15	200
209	228	502410	CTCAGCCGCACCTCGGCTGA	32	201
210	229	502411	CCTCAGCCGCACCTCGGCTG	65	202
211	230	502412	GCCTCAGCCGCACCTCGGCT	81	203
232	251	502413	CCAACACCAGCTGCTGGAGC	90	204
233	252	502414	TCCAACACCAGCTGCTGGAG	78	205
234	253	502415	GTCCAACACCAGCTGCTGGA	84	206
236	255	502416	GGGTCCAACACCAGCTGCTG	69	207
257	276	502417	GGCTCCAGCCCCAGGAAGCC	46	208
258	277	502418	GGGCTCCAGCCCCAGGAAGC	28	209
276	295	502419	CAGGAGAAGGTCGAGCAGGG	41	210
278	297	502420	CCCAGGAGAAGGTCGAGCAG	71	211
279	298	502421	GCCCAGGAGAAGGTCGAGCA	85	212
280	299	451363	CGCCCAGGAGAAGGTCGAGC	84	213
281	300	502422	ACGCCCAGGAGAAGGTCGAG	67	214
317	336	502423	TCCTGGGCCAGTTCGGAGGC	58	215
318	337	502424	GTCCTGGGCCAGTTCGGAGG	71	216
319	338	502425	TGTCCTGGGCCAGTTCGGAG	69	217
320	339	502426	TTGTCCTGGGCCAGTTCGGA	71	218
321	340	502427	CTTGTCCTGGGCCAGTTCGG	66	219
322	341	502428	ACTTGTCCTGGGCCAGTTCG	59	220
323	342	502429	TACTTGTCCTGGGCCAGTTC	75	221
324	343	502430	GTACTTGTCCTGGGCCAGTT	78	222
325	344	502431	CGTACTTGTCCTGGGCCAGT	74	223
343	362	502432	ACTGCAAGAAGTCGGCCACG	73	224
345	364	502433	CCACTGCAAGAAGTCGGCCA	65	225
346	365	451364	CCCACTGCAAGAAGTCGGCC	32	226
347	366	502434	GCCCACTGCAAGAAGTCGGC	70	227
348	367	502435	CGCCCACTGCAAGAAGTCGG	61	228
349	368	502436	CCGCCCACTGCAAGAAGTCG	54	229

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
350	369	502437	TCCGCCCACTGCAAGAAGTC	40	230
351	370	502438	CTCCGCCCACTGCAAGAAGT	33	231
352	371	502439	GCTCCGCCCACTGCAAGAAG	23	232
353	372	502440	GGCTCCGCCCACTGCAAGAA	23	233
354	373	502441	GGGCTCCGCCCACTGCAAGA	17	234
355	374	502442	TGGGCTCCGCCCACTGCAAG	22	235
356	375	502443	ATGGGCTCCGCCCACTGCAA	14	236
357	376	502444	GATGGGCTCCGCCCACTGCA	43	237
358	377	502445	CGATGGGCTCCGCCCACTGC	37	238
359	378	502446	ACGATGGGCTCCGCCCACTG	0	239
360	379	502447	CACGATGGGCTCCGCCCACT	59	240
361	380	502448	CCACGATGGGCTCCGCCCAC	69	241
362	381	502449	ACCACGATGGGCTCCGCCCA	63	242
363	382	502450	CACCACGATGGGCTCCGCCC	73	243
364	383	502451	TCACCACGATGGGCTCCGCC	77	244
365	384	502452	CTCACCACGATGGGCTCCGC	66	245
366	385	502453	CCTCACCACGATGGGCTCCG	81	246
367	386	502454	GCCTCACCACGATGGGCTCC	77	247
368	387	502455	AGCCTCACCACGATGGGCTC	63	248
369	388	502456	AAGCCTCACCACGATGGGCT	70	249
370	389	502457	TAAGCCTCACCACGATGGGC	78	250
371	390	502458	TTAAGCCTCACCACGATGGG	76	251
372	391	502459	CTTAAGCCTCACCACGATGG	78	252
373	392	502460	CCTTAAGCCTCACCACGATG	68	253
374	393	502461	TCCTTAAGCCTCACCACGAT	67	254
375	394	502462	CTCCTTAAGCCTCACCACGA	84	255
376	395	502463	CCTCCTTAAGCCTCACCACG	76	256
377	396	502464	ACCTCCTTAAGCCTCACCAC	64	257
378	397	502465	GACCTCCTTAAGCCTCACCA	72	258
379	398	502466	GGACCTCCTTAAGCCTCACC	69	259
380	399	502467	CGGACCTCCTTAAGCCTCAC	81	260
381	400	502468	TCGGACCTCCTTAAGCCTCA	78	261
382	401	502469	GTCGGACCTCCTTAAGCCTC	57	262
384	403	502470	CAGTCGGACCTCCTTAAGCC	62	263
385	404	502471	GCAGTCGGACCTCCTTAAGC	45	264

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
386	405	502472	TGCAGTCGGACCTCCTTAAG	60	265
412	431	502473	CCTTCAGAATCTCGAAGTCG	67	266
413	432	502474	ACCTTCAGAATCTCGAAGTC	50	267
415	434	502475	TCACCTTCAGAATCTCGAAG	54	268
416	435	502476	ATCACCTTCAGAATCTCGAA	38	269
417	436	502477	GATCACCTTCAGAATCTCGA	35	270
419	438	502478	CCGATCACCTTCAGAATCTC	52	271
420	439	502479	TCCGATCACCTTCAGAATCT	50	272
421	440	502480	GTCCGATCACCTTCAGAATC	44	273
422	441	502481	CGTCCGATCACCTTCAGAAT	41	274
467	486	502482	CCCGTCTGCTTCATCTTCAC	67	275
468	487	502483	GCCCGTCTGCTTCATCTTCA	76	276
469	488	502484	GGCCCGTCTGCTTCATCTTC	57	277
470	489	502485	TGGCCCGTCTGCTTCATCTT	64	278
471	490	502486	CTGGCCCGTCTGCTTCATCT	64	279
472	491	502487	CCTGGCCCGTCTGCTTCATC	73	280
473	492	502488	ACCTGGCCCGTCTGCTTCAT	64	281
474	493	502489	CACCTGGCCCGTCTGCTTCA	80	282
475	494	502490	ACACCTGGCCCGTCTGCTTC	71	283
476	495	502491	TACACCTGGCCCGTCTGCTT	74	284
497	516	502492	TTGTTCATGATCTTCATGGC	56	285
499	518	502493	ACTTGTTCATGATCTTCATG	23	286
500	519	502494	CACTTGTTCATGATCTTCAT	43	287
501	520	502495	CCACTTGTTCATGATCTTCA	43	288
502	521	502496	CCCACTTGTTCATGATCTTC	47	289
503	522	502497	TCCCACTTGTTCATGATCTT	34	290
504	523	502498	GTCCCACTTGTTCATGATCT	34	291
505	524	502499	TGTCCCACTTGTTCATGATC	27	292
506	525	502500	ATGTCCCACTTGTTCATGAT	23	293
507	526	502501	CATGTCCCACTTGTTCATGA	51	294
508	527	502502	GCATGTCCCACTTGTTCATG	20	295
509	528	502503	AGCATGTCCCACTTGTTCAT	52	296
510	529	502504	CAGCATGTCCCACTTGTTCA	72	297
511	530	502505	TCAGCATGTCCCACTTGTTC	70	298
512	531	502506	TTCAGCATGTCCCACTTGTT	53	299

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
513	532	502507	CTTCAGCATGTCCCACTTGT	52	300
514	533	502508	TCTTCAGCATGTCCCACTTG	45	301
516	535	502509	CCTCTTCAGCATGTCCCACT	68	302
517	536	502510	CCCTCTTCAGCATGTCCCAC	68	303
518	537	502511	CCCCTCTTCAGCATGTCCCA	79	304
519	538	502512	GCCCCTCTTCAGCATGTCCC	85	305
520	539	502513	CGCCCCTCTTCAGCATGTCC	84	306
521	540	502514	TCGCCCCTCTTCAGCATGTC	80	307
522	541	502515	CTCGCCCCTCTTCAGCATGT	82	308
523	542	502516	CCTCGCCCCTCTTCAGCATG	78	309
524	543	502517	ACCTCGCCCCTCTTCAGCAT	73	310
525	544	502518	CACCTCGCCCCTCTTCAGCA	76	311
526	545	502519	ACACCTCGCCCCTCTTCAGC	79	312
527	546	502520	GACACCTCGCCCCTCTTCAG	73	313
821	840	502521	GCCAGGCGGATGTGGCCACA	57	314
868	887	502522	ACCGCACCGTTCCATCTGCC	62	315
869	888	502523	GACCGCACCGTTCCATCTGC	29	316
923	942	502524	ACAGCCTGCAGGATCTCGGG	86	317
924	943	502525	CACAGCCTGCAGGATCTCGG	81	318
925	944	502526	CCACAGCCTGCAGGATCTCG	83	319
926	945	502527	CCCACAGCCTGCAGGATCTC	84	320
927	946	502528	GCCCACAGCCTGCAGGATCT	91	321
928	947	502529	CGCCCACAGCCTGCAGGATC	90	322
929	948	502530	CCGCCCACAGCCTGCAGGAT	82	323
930	949	502531	ACCGCCCACAGCCTGCAGGA	83	324
931	950	502532	CACCGCCCACAGCCTGCAGG	85	325
932	951	502533	CCACCGCCCACAGCCTGCAG	84	326
933	952	502534	CCCACCGCCCACAGCCTGCA	80	327
934	953	502535	GCCCACCGCCCACAGCCTGC	90	328
935	954	502536	GGCCCACCGCCCACAGCCTG	94	329
936	955	502537	AGGCCCACCGCCCACAGCCT	88	330
937	956	502538	CAGGCCCACCGCCCACAGCC	91	331
938	957	502539	CCAGGCCCACCGCCCACAGC	73	332
939	958	502540	CCCAGGCCCACCGCCCACAG	86	333
940	959	502541	TCCCAGGCCCACCGCCCACA	88	334

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
941	960	502542	GTCCCAGGCCCACCGCCCAC	84	335
942	961	502543	TGTCCCAGGCCCACCGCCCA	85	336
943	962	502544	CTGTCCCAGGCCCACCGCCC	65	337
944	963	502545	CCTGTCCCAGGCCCACCGCC	81	338
945	964	502546	GCCTGTCCCAGGCCCACCGC	90	339
946	965	502547	TGCCTGTCCCAGGCCCACCG	85	340
947	966	502548	CTGCCTGTCCCAGGCCCACC	89	341
948	967	502549	GCTGCCTGTCCCAGGCCCAC	91	342
949	968	502550	AGCTGCCTGTCCCAGGCCCA	94	343
950	969	502551	TAGCTGCCTGTCCCAGGCCC	92	344
951	970	502552	GTAGCTGCCTGTCCCAGGCC	88	345
952	971	502553	CGTAGCTGCCTGTCCCAGGC	85	346
953	972	502554	CCGTAGCTGCCTGTCCCAGG	83	347
954	973	502555	CCCGTAGCTGCCTGTCCCAG	64	348
955	974	502556	GCCCGTAGCTGCCTGTCCCA	83	349
956	975	502557	GGCCCGTAGCTGCCTGTCCC	89	350
1004	1023	502558	TAGAACATTTCATAGGCGAA	68	351
1042	1061	502559	TCTCCGCCGTGGAATCCGCG	75	352
1043	1062	502560	GTCTCCGCCGTGGAATCCGC	79	353
1044	1063	502561	GGTCTCCGCCGTGGAATCCG	66	354
1045	1064	502562	AGGTCTCCGCCGTGGAATCC	50	355
1046	1065	502563	TAGGTCTCCGCCGTGGAATC	71	356
1067	1086	502564	TTGTAGTGGACGATCTTGCC	68	357
1068	1087	502565	CTTGTAGTGGACGATCTTGC	70	358
1069	1088	502566	CCTTGTAGTGGACGATCTTG	61	359
1070	1089	502567	TCCTTGTAGTGGACGATCTT	72	360
1071	1090	502568	CTCCTTGTAGTGGACGATCT	75	361
1072	1091	502569	GCTCCTTGTAGTGGACGATC	75	362
1073	1092	502570	TGCTCCTTGTAGTGGACGAT	83	363
1074	1093	502571	GTGCTCCTTGTAGTGGACGA	72	364
1075	1094	502572	GGTGCTCCTTGTAGTGGACG	66	365
1076	1095	502573	AGGTGCTCCTTGTAGTGGAC	51	366
1077	1096	502574	GAGGTGCTCCTTGTAGTGGA	46	367
1078	1097	502575	AGAGGTGCTCCTTGTAGTGG	70	368
1079	1098	502576	GAGAGGTGCTCCTTGTAGTG	47	369

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1080	1099	502577	AGAGAGGTGCTCCTTGTAGT	65	370
1081	1100	502578	GAGAGAGGTGCTCCTTGTAG	45	371
1082	1101	502579	AGAGAGAGGTGCTCCTTGTA	63	372
1083	1102	502580	CAGAGAGAGGTGCTCCTTGT	77	373
1085	1104	502581	GGCAGAGAGAGGTGCTCCTT	70	374
1086	1105	502582	CGGCAGAGAGAGGTGCTCCT	80	375
1087	1106	502583	GCGGCAGAGAGAGGTGCTCC	62	376
1088	1107	502584	AGCGGCAGAGAGAGGTGCTC	44	377
1089	1108	502585	CAGCGGCAGAGAGAGGTGCT	78	378
1090	1109	502586	CCAGCGGCAGAGAGAGGTGC	71	379
1165	1184	502587	GGCCCAGCCGTGTCTCCGGG	77	380
1166	1185	502588	CGGCCCAGCCGTGTCTCCGG	69	381
1167	1186	502589	CCGGCCCAGCCGTGTCTCCG	70	382
1168	1187	502590	CCCGGCCCAGCCGTGTCTCC	75	383
1169	1188	502591	CCCCGGCCCAGCCGTGTCTC	77	384
1170	1189	502592	ACCCCGGCCCAGCCGTGTCT	73	385
1171	1190	502593	CACCCCGGCCCAGCCGTGTC	84	386
1172	1191	502594	CCACCCCGGCCCAGCCGTGT	78	387
1173	1192	502595	TCCACCCCGGCCCAGCCGTG	71	388
1174	1193	502596	CTCCACCCCGGCCCAGCCGT	81	389
1175	1194	502597	GCTCCACCCCGGCCCAGCCG	86	390
1176	1195	502598	TGCTCCACCCCGGCCCAGCC	83	391
1177	1196	502599	CTGCTCCACCCCGGCCCAGC	88	392
1199	1218	502600	AAGGGATGTGTCCGGAAGTC	60	393
1200	1219	502601	GAAGGGATGTGTCCGGAAGT	58	394
1201	1220	502602	AGAAGGGATGTGTCCGGAAG	63	395
1202	1221	502603	AAGAAGGGATGTGTCCGGAA	62	396
1203	1222	502604	GAAGAAGGGATGTGTCCGGA	61	397
1204	1223	502605	AGAAGAAGGGATGTGTCCGG	62	398
1205	1224	502606	AAGAAGAAGGGATGTGTCCG	56	399
1206	1225	502607	AAAGAAGAAGGGATGTGTCC	58	400
1207	1226	502608	CAAAGAAGAAGGGATGTGTC	50	401
1208	1227	502609	CCAAAGAAGAAGGGATGTGT	61	402
1210	1229	502610	GGCCAAAGAAGAAGGGATGT	73	403
1211	1230	502611	AGGCCAAAGAAGAAGGGATG	56	404

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1212	1231	502612	GAGGCCAAAGAAGAAGGGAT	73	405
1213	1232	502613	CGAGGCCAAAGAAGAAGGGA	75	406
1214	1233	502614	TCGAGGCCAAAGAAGAAGGG	75	407
1215	1234	502615	GTCGAGGCCAAAGAAGAAGG	83	408
1216	1235	502616	AGTCGAGGCCAAAGAAGAAG	58	409
1217	1236	502617	CAGTCGAGGCCAAAGAAGAA	52	410
1218	1237	502618	CCAGTCGAGGCCAAAGAAGA	68	411
1219	1238	502619	CCCAGTCGAGGCCAAAGAAG	78	412
1220	1239	502620	TCCCAGTCGAGGCCAAAGAA	66	413
1221	1240	502621	ATCCCAGTCGAGGCCAAAGA	75	414
1222	1241	502622	CATCCCAGTCGAGGCCAAAG	70	415
1223	1242	502623	CCATCCCAGTCGAGGCCAAA	81	416
1224	1243	502624	ACCATCCCAGTCGAGGCCAA	82	417
1225	1244	502625	GACCATCCCAGTCGAGGCCA	88	418
1226	1245	502626	AGACCATCCCAGTCGAGGCC	79	419
1227	1246	502627	GAGACCATCCCAGTCGAGGC	82	420
1228	1247	502628	GGAGACCATCCCAGTCGAGG	60	421
1263	1282	502629	TTCGAAATCCGGTGTAAAGG	84	422
1264	1283	502630	CTTCGAAATCCGGTGTAAAG	57	423
1265	1284	502631	CCTTCGAAATCCGGTGTAAA	64	424
1266	1285	502632	ACCTTCGAAATCCGGTGTAA	73	425
1267	1286	502633	CACCTTCGAAATCCGGTGTA	77	426
1268	1287	502634	GCACCTTCGAAATCCGGTGT	59	427
1269	1288	502635	GGCACCTTCGAAATCCGGTG	85	428
1270	1289	502636	TGGCACCTTCGAAATCCGGT	86	429
1271	1290	502637	GTGGCACCTTCGAAATCCGG	74	430
1272	1291	502638	GGTGGCACCTTCGAAATCCG	79	431
1273	1292	502639	CGGTGGCACCTTCGAAATCC	85	432
1274	1293	502640	TCGGTGGCACCTTCGAAATC	71	433
1275	1294	502641	GTCGGTGGCACCTTCGAAAT	88	434
1276	1295	502642	TGTCGGTGGCACCTTCGAAA	89	435
1277	1296	502643	GTGTCGGTGGCACCTTCGAA	88	436
1278	1297	502644	TGTGTCGGTGGCACCTTCGA	87	437
1279	1298	502645	ATGTGTCGGTGGCACCTTCG	88	438
1280	1299	502646	CATGTGTCGGTGGCACCTTC	88	439

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1281	1300	502647	GCATGTGTCGGTGGCACCTT	91	440
1282	1301	502648	TGCATGTGTCGGTGGCACCT	87	441
1283	1302	502649	TTGCATGTGTCGGTGGCACC	86	442
1284	1303	502650	GTTGCATGTGTCGGTGGCAC	83	443
1285	1304	502651	AGTTGCATGTGTCGGTGGCA	81	444
1286	1305	502652	AAGTTGCATGTGTCGGTGGC	79	445
1287	1306	502653	GAAGTTGCATGTGTCGGTGG	58	446
1288	1307	502654	CGAAGTTGCATGTGTCGGTG	85	447
1290	1309	502655	GTCGAAGTTGCATGTGTCGG	77	448
1291	1310	502656	AGTCGAAGTTGCATGTGTCG	79	449
1292	1311	502657	AAGTCGAAGTTGCATGTGTC	74	450
1293	1312	502658	CAAGTCGAAGTTGCATGTGT	82	451
1294	1313	502659	CCAAGTCGAAGTTGCATGTG	82	452
1295	1314	502660	ACCAAGTCGAAGTTGCATGT	70	453
1296	1315	502661	CACCAAGTCGAAGTTGCATG	76	454
1297	1316	502662	CCACCAAGTCGAAGTTGCAT	79	455
1298	1317	502663	TCCACCAAGTCGAAGTTGCA	68	456
1299	1318	502664	CTCCACCAAGTCGAAGTTGC	71	457
1300	1319	502665	CCTCCACCAAGTCGAAGTTG	67	458
1301	1320	502666	TCCTCCACCAAGTCGAAGTT	70	459
1302	1321	502667	GTCCTCCACCAAGTCGAAGT	80	460
1303	1322	502668	CGTCCTCCACCAAGTCGAAG	76	461
1304	1323	502669	CCGTCCTCCACCAAGTCGAA	78	462
1305	1324	502670	CCCGTCCTCCACCAAGTCGA	83	463
1306	1325	502671	GCCCGTCCTCCACCAAGTCG	76	464
1307	1326	502672	AGCCCGTCCTCCACCAAGTC	72	465
1308	1327	502673	GAGCCCGTCCTCCACCAAGT	71	466
1309	1328	502674	TGAGCCCGTCCTCCACCAAG	60	467
1702	1721	502675	GGTTCCGAGCCTCTGCCTCG	44	468
1703	1722	502676	CGGTTCCGAGCCTCTGCCTC	74	469
1704	1723	502677	CCGGTTCCGAGCCTCTGCCT	72	470
1705	1724	502678	CCCGGTTCCGAGCCTCTGCC	73	471
1706	1725	502679	TCCCGGTTCCGAGCCTCTGC	84	472
1707	1726	502680	GTCCCGGTTCCGAGCCTCTG	66	473
1709	1728	502681	AGGTCCCGGTTCCGAGCCTC	82	474

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1710	1729	502682	TAGGTCCCGGTTCCGAGCCT	83	475
1711	1730	502683	CTAGGTCCCGGTTCCGAGCC	81	476
1712	1731	502684	TCTAGGTCCCGGTTCCGAGC	74	477
1713	1732	502685	CTCTAGGTCCCGGTTCCGAG	78	478
1714	1733	502686	CCTCTAGGTCCCGGTTCCGA	75	479
1715	1734	502687	GCCTCTAGGTCCCGGTTCCG	80	480
1743	1762	502688	CATCCGCTCCTGCAACTGCC	89	481
1744	1763	502689	CCATCCGCTCCTGCAACTGC	81	482
1745	1764	502690	TCCATCCGCTCCTGCAACTG	71	483
1746	1765	502691	CTCCATCCGCTCCTGCAACT	75	484
1747	1766	502692	ACTCCATCCGCTCCTGCAAC	64	485
1748	1767	502693	AACTCCATCCGCTCCTGCAA	52	486
1749	1768	502694	CAACTCCATCCGCTCCTGCA	45	487
1751	1770	502695	AGCAACTCCATCCGCTCCTG	78	488
1752	1771	502696	CAGCAACTCCATCCGCTCCT	64	489
1753	1772	502697	GCAGCAACTCCATCCGCTCC	56	490
1774	1793	502698	CAGCTGTGGCTCCCTCTGCC	60	491
1775	1794	502699	ACAGCTGTGGCTCCCTCTGC	45	492
1776	1795	502700	GACAGCTGTGGCTCCCTCTG	49	493
1777	1796	502701	TGACAGCTGTGGCTCCCTCT	26	494
1778	1797	502702	GTGACAGCTGTGGCTCCCTC	32	495
1779	1798	502703	CGTGACAGCTGTGGCTCCCT	28	496
1780	1799	502704	CCGTGACAGCTGTGGCTCCC	35	497
1781	1800	502705	CCCGTGACAGCTGTGGCTCC	33	498
1782	1801	502706	CCCCGTGACAGCTGTGGCTC	53	499
1783	1802	502707	CCCCCGTGACAGCTGTGGCT	39	500
1784	1803	502708	ACCCCCGTGACAGCTGTGGC	53	501
1785	1804	502709	GACCCCCGTGACAGCTGTGG	51	502
1786	1805	502710	GGACCCCCGTGACAGCTGTG	58	503
1787	1806	502711	GGGACCCCCGTGACAGCTGT	71	504
1814	1833	502712	GAAGGTGGATCCGTGGCCCG	73	505
1815	1834	502713	GGAAGGTGGATCCGTGGCCC	70	506
1816	1835	502714	GGGAAGGTGGATCCGTGGCC	72	507
1817	1836	502715	TGGGAAGGTGGATCCGTGGC	50	508
1818	1837	502716	ATGGGAAGGTGGATCCGTGG	62	509

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1819	1838	502717	GATGGGAAGGTGGATCCGTG	75	510
1821	1840	502718	TAGATGGGAAGGTGGATCCG	52	511
1822	1841	502719	CTAGATGGGAAGGTGGATCC	56	512
1823	1842	502720	TCTAGATGGGAAGGTGGATC	21	513
1824	1843	502721	ATCTAGATGGGAAGGTGGAT	34	514
1826	1845	502722	CCATCTAGATGGGAAGGTGG	43	515
1827	1846	502723	GCCATCTAGATGGGAAGGTG	17	516
1828	1847	451383	GGCCATCTAGATGGGAAGGT	0	517
1863	1882	502724	CACCAGCGGGCACTGGCCCA	51	518
1864	1883	502725	CCACCAGCGGGCACTGGCCC	55	519
1865	1884	502726	CCCACCAGCGGGCACTGGCC	61	520
1866	1885	502727	CCCCACCAGCGGGCACTGGC	43	521
1868	1887	502728	GGCCCCACCAGCGGGCACTG	16	522
1869	1888	502729	TGGCCCCACCAGCGGGCACT	43	523
1870	1889	502730	CTGGCCCCACCAGCGGGCAC	43	524
1871	1890	502731	CCTGGCCCCACCAGCGGGCA	41	525
1872	1891	502732	GCCTGGCCCCACCAGCGGGC	30	526
1874	1893	502733	GGGCCTGGCCCCACCAGCGG	66	527
1892	1911	502734	AGGTGGCGGCGGTGCATGGG	31	528
1893	1912	502735	CAGGTGGCGGCGGTGCATGG	23	529
1894	1913	502736	GCAGGTGGCGGCGGTGCATG	57	530
1895	1914	502737	AGCAGGTGGCGGCGGTGCAT	54	531
1896	1915	502738	CAGCAGGTGGCGGCGGTGCA	61	532
1897	1916	502739	GCAGCAGGTGGCGGCGGTGC	57	533
1898	1917	502740	AGCAGCAGGTGGCGGCGGTG	36	534
1899	1918	502741	GAGCAGCAGGTGGCGGCGGT	53	535
1900	1919	502742	GGAGCAGCAGGTGGCGGCGG	39	536
1901	1920	502743	GGGAGCAGCAGGTGGCGGCG	36	537
1902	1921	502744	AGGGAGCAGCAGGTGGCGGC	62	538
1903	1922	502745	CAGGGAGCAGCAGGTGGCGG	56	539
1904	1923	502746	GCAGGGAGCAGCAGGTGGCG	58	540
1905	1924	502747	GGCAGGGAGCAGCAGGTGGC	65	541
1906	1925	502748	TGGCAGGGAGCAGCAGGTGG	47	542
1907	1926	502749	CTGGCAGGGAGCAGCAGGTG	41	543
1909	1928	451432	CCCTGGCAGGGAGCAGCAGG	53	544

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1910	1929	502750	ACCCTGGCAGGGAGCAGCAG	52	545
1911	1930	502751	GACCCTGGCAGGGAGCAGCA	77	546
1912	1931	502752	GGACCCTGGCAGGGAGCAGC	0	547
1919	1938	502753	GGCCTAGGGACCCTGGCAGG	39	548
1920	1939	502754	AGGCCTAGGGACCCTGGCAG	35	549
1922	1941	502755	CCAGGCCTAGGGACCCTGGC	44	550
1923	1942	502756	GCCAGGCCTAGGGACCCTGG	60	551
1924	1943	502757	GGCCAGGCCTAGGGACCCTG	58	552
1925	1944	502758	AGGCCAGGCCTAGGGACCCT	57	553
1926	1945	502759	TAGGCCAGGCCTAGGGACCC	52	554
1927	1946	502760	ATAGGCCAGGCCTAGGGACC	51	555
1928	1947	502761	GATAGGCCAGGCCTAGGGAC	41	556
1929	1948	502762	CGATAGGCCAGGCCTAGGGA	69	557
1930	1949	502763	CCGATAGGCCAGGCCTAGGG	80	558
1931	1950	502764	TCCGATAGGCCAGGCCTAGG	78	559
1932	1951	502765	CTCCGATAGGCCAGGCCTAG	89	560
1933	1952	502766	CCTCCGATAGGCCAGGCCTA	79	561
1934	1953	502767	GCCTCCGATAGGCCAGGCCT	73	562
1936	1955	502768	GCGCCTCCGATAGGCCAGGC	83	563
1952	1971	502769	AACAGGAGCAGGGAAAGCGC	83	564
1953	1972	502770	GAACAGGAGCAGGGAAAGCG	70	565
1954	1973	502771	CGAACAGGAGCAGGGAAAGC	43	566
1955	1974	502772	GCGAACAGGAGCAGGGAAAG	47	567
1956	1975	502773	GGCGAACAGGAGCAGGGAAA	61	568
1957	1976	502774	CGGCGAACAGGAGCAGGGAA	74	569
1958	1977	502775	ACGGCGAACAGGAGCAGGGA	60	570
1959	1978	502776	AACGGCGAACAGGAGCAGGG	86	571
1960	1979	502777	CAACGGCGAACAGGAGCAGG	84	572
1981	2000	502778	GGGCGGCGGCACGAGACAGA	80	573
1982	2001	502779	AGGGCGGCGGCACGAGACAG	76	574
1983	2002	502780	CAGGGCGGCGGCACGAGACA	58	575
1984	2003	502781	CCAGGGCGGCGGCACGAGAC	80	576
1985	2004	502782	CCCAGGGCGGCGGCACGAGA	59	577
1986	2005	502783	GCCCAGGGCGGCGGCACGAG	68	578
1987	2006	502784	AGGCCAGGGCGGCGGCACGA	75	579

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1988	2007	502785	CAGCCCAGGGCGGCGGCACG	76	580
1989	2008	502786	GCAGCCCAGGGCGGCGGCAC	70	581
2026	2045	502787	CTGCGGTGAGTTGGCCGGCG	68	582
2027	2046	502788	ACTGCGGTGAGTTGGCCGGC	67	583
2028	2047	502789	GACTGCGGTGAGTTGGCCGG	58	584
2029	2048	502790	AGACTGCGGTGAGTTGGCCG	71	585
2030	2049	502791	CAGACTGCGGTGAGTTGGCC	70	586
2031	2050	502792	CCAGACTGCGGTGAGTTGGC	79	587
2032	2051	502793	GCCAGACTGCGGTGAGTTGG	76	588
2033	2052	502794	CGCCAGACTGCGGTGAGTTG	66	589
2077	2096	502795	AAGACAGTTCTAGGGTTCAG	87	590
2078	2097	502796	GAAGACAGTTCTAGGGTTCA	78	591
2079	2098	502797	CGAAGACAGTTCTAGGGTTC	85	592
2080	2099	502798	TCGAAGACAGTTCTAGGGTT	78	593
2081	2100	502799	GTCGAAGACAGTTCTAGGGT	92	594
2082	2101	502800	AGTCGAAGACAGTTCTAGGG	85	595
2083	2102	502801	GAGTCGAAGACAGTTCTAGG	83	596
2084	2103	502802	GGAGTCGAAGACAGTTCTAG	86	597
2085	2104	502803	CGGAGTCGAAGACAGTTCTA	91	598
2086	2105	502804	CCGGAGTCGAAGACAGTTCT	76	599
2087	2106	502805	CCCGGAGTCGAAGACAGTTC	90	600
2088	2107	502806	CCCCGGAGTCGAAGACAGTT	83	601

TABLE 12-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 1

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
2089	2108	502807	GCCCCGGAGTCGAAGACAGT	82	602
2090	2109	502808	GGCCCCGGAGTCGAAGACAG	73	603
2091	2110	502809	GGGCCCCGGAGTCGAAGACA	67	604
2143	2162	502810	AGGCGGTGGGCGCGGCTTCT	73	605
2144	2163	502811	CAGGCGGTGGGCGCGGCTTC	57	606
2145	2164	502812	GCAGGCGGTGGGCGCGGCTT	69	607
2147	2166	502813	TGGCAGGCGGTGGGCGCGGC	73	608
2149	2168	502814	ACTGGCAGGCGGTGGGCGCG	56	609
2151	2170	502815	GAACTGGCAGGCGGTGGGCG	71	610
2152	2171	502816	TGAACTGGCAGGCGGTGGGC	80	611
2154	2173	502817	TGTGAACTGGCAGGCGGTGG	85	612
2187	2206	502818	TGGAGCTGGGCGGAGACCCA	55	613
2189	2208	502819	ACTGGAGCTGGGCGGAGACC	53	614
2190	2209	502820	GACTGGAGCTGGGCGGAGAC	55	615
2192	2211	502821	AGGACTGGAGCTGGGCGGAG	76	616
2194	2213	502822	ACAGGACTGGAGCTGGGCGG	77	617
2195	2214	502823	CACAGGACTGGAGCTGGGCG	74	618
2196	2215	502824	TCACAGGACTGGAGCTGGGC	90	619
2386	2405	502825	GCCTCAGCCTGGCCGAAAGA	80	620
2387	2406	502826	GGCCTCAGCCTGGCCGAAAG	72	621
2490	2509	444401	TTGCACTTTGCGAACCAACG	97	41

TABLE 13

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
503	522	502983	TGGTGGAGCCAAGCCCTCCC	83	622
561	580	502984	GGGCACCCTCAGAGCCTGAA	82	623
1197	1216	502369	GCCTGGCAGCCCCTGTCCAG	16	160
1198	1217	502370	GGCCTGGCAGCCCCTGTCCA	58	161
1199	1218	502371	GGGCCTGGCAGCCCCTGTCC	62	162
1242	1261	502372	ATGGCCCCTCCCCGGGCCGG	41	163
1243	1262	502373	CATGGCCCCTCCCCGGGCCG	29	164
1244	1263	502374	CCATGGCCCCTCCCCGGGCC	34	165

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1245	1264	502375	ACCATGGCCCCTCCCCGGGC	60	166
1246	1265	502376	CACCATGGCCCCTCCCCGGG	68	167
1247	1266	502377	GCACCATGGCCCCTCCCCGG	75	168
1248	1267	502378	AGCACCATGGCCCCTCCCCG	65	169
1249	1268	502379	CAGCACCATGGCCCCTCCCC	63	170
1250	1269	502380	GCAGCACCATGGCCCCTCCC	73	171
1251	1270	502381	GGCAGCACCATGGCCCCTCC	80	172
1253	1272	502382	CAGGCAGCACCATGGCCCCT	82	173
1254	1273	502383	ACAGGCAGCACCATGGCCCC	72	174
1256	1275	502384	GGACAGGCAGCACCATGGCC	70	175
1257	1276	502385	TGGACAGGCAGCACCATGGC	71	176
1258	1277	502386	TTGGACAGGCAGCACCATGG	73	177
1259	1278	502387	GTTGGACAGGCAGCACCATG	73	178
1260	1279	502388	TGTTGGACAGGCAGCACCAT	60	179
1261	1280	502389	ATGTTGGACAGGCAGCACCA	75	180
1262	1281	502390	CATGTTGGACAGGCAGCACC	81	181
1263	1282	502391	ACATGTTGGACAGGCAGCAC	67	182
1264	1283	502392	GACATGTTGGACAGGCAGCA	71	183
1265	1284	502393	TGACATGTTGGACAGGCAGC	81	184
1266	1285	502394	CTGACATGTTGGACAGGCAG	76	185
1267	1286	502395	GCTGACATGTTGGACAGGCA	70	186
1268	1287	502396	GGCTGACATGTTGGACAGGC	77	187
1269	1288	502397	CGGCTGACATGTTGGACAGG	74	188
1270	1289	502398	TCGGCTGACATGTTGGACAG	63	189
1271	1290	502399	CTCGGCTGACATGTTGGACA	80	190
1272	1291	502400	CCTCGGCTGACATGTTGGAC	71	191
1273	1292	502401	ACCTCGGCTGACATGTTGGA	64	192
1274	1293	502402	CACCTCGGCTGACATGTTGG	71	193
1275	1294	502403	GCACCTCGGCTGACATGTTG	77	194
1276	1295	502404	CGCACCTCGGCTGACATGTT	80	195
1277	1296	502405	CCGCACCTCGGCTGACATGT	80	196
1278	1297	502406	GCCGCACCTCGGCTGACATG	79	197
1279	1298	502407	AGCCGCACCTCGGCTGACAT	74	198
1280	1299	502408	CAGCCGCACCTCGGCTGACA	66	199
1281	1300	502409	TCAGCCGCACCTCGGCTGAC	15	200
1282	1301	502410	CTCAGCCGCACCTCGGCTGA	32	201

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1283	1302	502411	CCTCAGCCGCACCTCGGCTG	65	202
1284	1303	502412	GCCTCAGCCGCACCTCGGCT	81	203
1305	1324	502413	CCAACACCAGCTGCTGGAGC	90	204
1306	1325	502414	TCCAACACCAGCTGCTGGAG	78	205
1307	1326	502415	GTCCAACACCAGCTGCTGGA	84	206
1309	1328	502416	GGGTCCAACACCAGCTGCTG	69	207
1330	1349	502417	GGCTCCAGCCCCAGGAAGCC	46	208
1331	1350	502418	GGGCTCCAGCCCCAGGAAGC	28	209
1349	1368	502419	CAGGAGAAGGTCGAGCAGGG	41	210
1351	1370	502420	CCCAGGAGAAGGTCGAGCAG	71	211
1352	1371	502421	GCCCAGGAGAAGGTCGAGCA	85	212
1353	1372	451363	CGCCCAGGAGAAGGTCGAGC	84	213
1354	1373	502422	ACGCCCAGGAGAAGGTCGAG	67	214
1390	1409	502423	TCCTGGGCCAGTTCGGAGGC	58	215
1391	1410	502424	GTCCTGGGCCAGTTCGGAGG	71	216
1392	1411	502425	TGTCCTGGGCCAGTTCGGAG	69	217
1393	1412	502426	TTGTCCTGGGCCAGTTCGGA	71	218
1394	1413	502427	CTTGTCCTGGGCCAGTTCGG	66	219
1395	1414	502428	ACTTGTCCTGGGCCAGTTCG	59	220
1396	1415	502429	TACTTGTCCTGGGCCAGTTC	75	221
1397	1416	502430	GTACTTGTCCTGGGCCAGTT	78	222
1398	1417	502431	CGTACTTGTCCTGGGCCAGT	74	223
1416	1435	502432	ACTGCAAGAAGTCGGCCACG	73	224
1418	1437	502433	CCACTGCAAGAAGTCGGCCA	65	225
1419	1438	451364	CCCACTGCAAGAAGTCGGCC	32	226
1421	1440	502985	ACCCCACTGCAAGAAGTCGG	60	624
1551	1570	502986	GCCCCAGGATGGGAGGATCT	58	625
1597	1616	502987	CATAGGACAGAGAAATGTTG	70	626
1630	1649	502988	TGCTGACCTTACTCTGCCCC	86	627
1666	1685	502989	TAAGCCATGGCTCTGAGTCA	51	628
1712	1731	502990	AGAGAGGCCATGGGAGGCTG	42	629
1841	1860	502991	CTGGCCCTCCTGGCTTGCCC	72	630
1853	1872	502992	AGCTGCCCCATGCTGGCCCT	76	631
1862	1881	502993	GCCCCTGGCAGCTGCCCCAT	70	632
1873	1892	502994	CTGTCGGCTGCGCCCCTGGC	78	633

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
1887	1906	502995	CGCCGAACACCTGCCTGTCG	68	634
1931	1950	502996	CCTCCCAGTGCCTGGGCACC	52	635
1981	2000	502998	GCGCCTGTCTGCAAAGCTGG	84	636
2025	2044	502999	CCCAAAGTTGTCCCTCCTGG	83	637
2038	2057	503000	ACACCCAGAAGAACCCAAAG	75	638
2117	2136	503001	CTGACCCACACGGCTCATAG	65	639
2235	2254	503002	TGGCCCCAGGCCCTGGAAAG	67	640
2278	2297	503003	GACAAGGCAGCTGGCAGAAG	79	641
2331	2350	503004	AAGAAACCAGTGACCAGTGA	85	642
2523	2542	503005	CTGTGAAATGGGAGGAGGAG	0	643
2578	2597	503006	GAAGGTTTTTCCAGAGGCTG	88	644
2615	2634	503007	GGCCAGGAGAGTCATTAGGG	84	645
2710	2729	503008	CCACAAAAGGAGTGCTCCTC	79	646
2789	2808	503009	CCTTTTAAGGCAGCAGGAAC	78	647
3629	3648	503010	CTAGGACTGTCTGCTTCCCA	88	648
3761	3780	502452	CTCACCACGATGGGCTCCGC	66	245
3762	3781	502453	CCTCACCACGATGGGCTCCG	81	246
3763	3782	502454	GCCTCACCACGATGGGCTCC	77	247
3764	3783	502455	AGCCTCACCACGATGGGCTC	63	248
3765	3784	502456	AAGCCTCACCACGATGGGCT	70	249
3766	3785	502457	TAAGCCTCACCACGATGGGC	78	250
3767	3786	502458	TTAAGCCTCACCACGATGGG	76	251
3768	3787	502459	CTTAAGCCTCACCACGATGG	78	252
3769	3788	502460	CCTTAAGCCTCACCACGATG	68	253
3770	3789	502461	TCCTTAAGCCTCACCACGAT	67	254
3771	3790	502462	CTCCTTAAGCCTCACCACGA	84	255
3772	3791	502463	CCTCCTTAAGCCTCACCACG	76	256
3773	3792	502464	ACCTCCTTAAGCCTCACCAC	64	257
3774	3793	502465	GACCTCCTTAAGCCTCACCA	72	258
3775	3794	502466	GGACCTCCTTAAGCCTCACC	69	259
3776	3795	502467	CGGACCTCCTTAAGCCTCAC	81	260
3777	3796	502468	TCGGACCTCCTTAAGCCTCA	78	261
3778	3797	502469	GTCGGACCTCCTTAAGCCTC	57	262
3780	3799	502470	CAGTCGGACCTCCTTAAGCC	62	263
3781	3800	502471	GCAGTCGGACCTCCTTAAGC	45	264
3782	3801	502472	TGCAGTCGGACCTCCTTAAG	60	265

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
3808	3827	502473	CCTTCAGAATCTCGAAGTCG	67	266
3809	3828	502474	ACCTTCAGAATCTCGAAGTC	50	267
3811	3830	502475	TCACCTTCAGAATCTCGAAG	54	268
3812	3831	502476	ATCACCTTCAGAATCTCGAA	38	269
3813	3832	502477	GATCACCTTCAGAATCTCGA	35	270
3815	3834	502478	CCGATCACCTTCAGAATCTC	52	271
3816	3835	502479	TCCGATCACCTTCAGAATCT	50	272
3817	3836	502480	GTCCGATCACCTTCAGAATC	44	273
3818	3837	502481	CGTCCGATCACCTTCAGAAT	41	274
3921	3940	503011	GTCATTCATCAATTTCTAAG	44	649
4118	4137	502482	CCCGTCTGCTTCATCTTCAC	67	275
4119	4138	502483	GCCCGTCTGCTTCATCTTCA	76	276
4120	4139	502484	GGCCCGTCTGCTTCATCTTC	57	277
4121	4140	502485	TGGCCCGTCTGCTTCATCTT	64	278
4122	4141	502486	CTGGCCCGTCTGCTTCATCT	64	279
4123	4142	502487	CCTGGCCCGTCTGCTTCATC	73	280
4124	4143	502488	ACCTGGCCCGTCTGCTTCAT	64	281
4125	4144	502489	CACCTGGCCCGTCTGCTTCA	80	282
4126	4145	502490	ACACCTGGCCCGTCTGCTTC	71	283
4127	4146	502491	TACACCTGGCCCGTCTGCTT	74	284
4148	4167	502492	TTGTTCATGATCTTCATGGC	56	285
4150	4169	502493	ACTTGTTCATGATCTTCATG	23	286
4151	4170	502494	CACTTGTTCATGATCTTCAT	43	287
4152	4171	502495	CCACTTGTTCATGATCTTCA	43	288
4153	4172	502496	CCCACTTGTTCATGATCTTC	47	289
4154	4173	502497	TCCCACTTGTTCATGATCTT	34	290
4155	4174	502498	GTCCCACTTGTTCATGATCT	34	291
4156	4175	502499	TGTCCCACTTGTTCATGATC	27	292
4157	4176	502500	ATGTCCCACTTGTTCATGAT	23	293
4158	4177	502501	CATGTCCCACTTGTTCATGA	51	294
4159	4178	502502	GCATGTCCCACTTGTTCATG	20	295
4160	4179	502503	AGCATGTCCCACTTGTTCAT	52	296
4161	4180	502504	CAGCATGTCCCACTTGTTCA	72	297
4162	4181	502505	TCAGCATGTCCCACTTGTTC	70	298
4163	4182	502506	TTCAGCATGTCCCACTTGTT	53	299

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
4164	4183	502507	CTTCAGCATGTCCCACTTGT	52	300
4165	4184	502508	TCTTCAGCATGTCCCACTTG	45	301
4167	4186	502509	CCTCTTCAGCATGTCCCACT	68	302
4168	4187	502510	CCCTCTTCAGCATGTCCCAC	68	303
4169	4188	502511	CCCCTCTTCAGCATGTCCCA	79	304
4170	4189	502512	GCCCCTCTTCAGCATGTCCC	85	305
4171	4190	502513	CGCCCCTCTTCAGCATGTCC	84	306
4172	4191	502514	TCGCCCCTCTTCAGCATGTC	80	307
4173	4192	502515	CTCGCCCCTCTTCAGCATGT	82	308
4174	4193	502516	CCTCGCCCCTCTTCAGCATG	78	309
4175	4194	502517	ACCTCGCCCCTCTTCAGCAT	73	310
4176	4195	502518	CACCTCGCCCCTCTTCAGCA	76	311
4239	4258	503012	GGAGGAGCTGCAGCCGGAGA	7	650
4245	4264	503013	GCACCCGGAGGAGCTGCAGC	0	651
4261	4280	503014	GCACGACACCTGCAGGGCAC	23	652
4355	4374	503015	AGCTCACCAGGTAGTTCTCA	49	653
4427	4446	503016	GCTTCCTCTCCCCACCTCCT	65	654
4447	4466	503017	GCAGCACCCCCAATCCTAGA	67	655
4508	4527	503018	GCCCCTCATCCACCTGACAC	62	656
4613	4632	503019	TTCCAGGTAAGAGACCCCCC	87	657
4679	4698	503020	AGAATAGGTCCCAGACACTC	81	658
4731	4750	503021	CTCCCCCTGAGATGTTCTGG	53	659
4858	4877	503022	CCCCAGCCCAGAGATAACCA	74	660
4927	4946	503023	CCTGATCCATCACGGATGGC	69	661
4987	5006	503024	TACTCCATGACCAGGTACTG	81	662
5185	5204	503025	GCTCTGACCTTCCAAGAACC	56	663
5354	5373	503026	CTCCCTTCTGTGGTCCCACC	0	664
5407	5426	503027	GTCGGGTTTGATGTCCCTGC	75	665
5445	5464	502521	GCCAGGCGGATGTGGCCACA	57	314
5500	5519	503028	AGGGCACTGGCTCACCGTTC	45	666
5681	5700	503029	GGGCCCTCCTTCCAACCACT	28	667
5708	5727	503030	GCCCACCCCTCTGGGCCCAC	45	668
5728	5747	503031	AGGAGCAGAGCGAGGCTTGG	38	669
5800	5819	502524	ACAGCCTGCAGGATCTCGGG	86	317
5801	5820	502525	CACAGCCTGCAGGATCTCGG	81	318
5802	5821	502526	CCACAGCCTGCAGGATCTCG	83	319

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
5803	5822	502527	CCCACAGCCTGCAGGATCTC	84	320
5804	5823	502528	GCCCACAGCCTGCAGGATCT	91	321
5805	5824	502529	CGCCCACAGCCTGCAGGATC	90	322
5806	5825	502530	CCGCCCACAGCCTGCAGGAT	82	323
5807	5826	502531	ACCGCCCACAGCCTGCAGGA	83	324
5808	5827	502532	CACCGCCCACAGCCTGCAGG	85	325
5809	5828	502533	CCACCGCCCACAGCCTGCAG	84	326
5810	5829	502534	CCCACCGCCCACAGCCTGCA	80	327
5811	5830	502535	GCCCACCGCCCACAGCCTGC	90	328
5812	5831	502536	GGCCCACCGCCCACAGCCTG	94	329
5813	5832	502537	AGGCCCACCGCCCACAGCCT	88	330
5814	5833	502538	CAGGCCCACCGCCCACAGCC	91	331
5815	5834	502539	CCAGGCCCACCGCCCACAGC	73	332
5816	5835	502540	CCCAGGCCCACCGCCCACAG	86	333
5817	5836	502541	TCCCAGGCCCACCGCCCACA	88	334
5818	5837	502542	GTCCCAGGCCCACCGCCCAC	84	335
5819	5838	502543	TGTCCCAGGCCCACCGCCCA	85	336
5820	5839	502544	CTGTCCCAGGCCCACCGCCC	65	337
5821	5840	502545	CCTGTCCCAGGCCCACCGCC	81	338
5822	5841	502546	GCCTGTCCCAGGCCCACCGC	90	339
5823	5842	502547	TGCCTGTCCCAGGCCCACCG	85	340
5824	5843	502548	CTGCCTGTCCCAGGCCCACC	89	341
5825	5844	502549	GCTGCCTGTCCCAGGCCCAC	91	342
5826	5845	502550	AGCTGCCTGTCCCAGGCCCA	94	343
5827	5846	502551	TAGCTGCCTGTCCCAGGCCC	92	344
5828	5847	502552	GTAGCTGCCTGTCCCAGGCC	88	345
5829	5848	502553	CGTAGCTGCCTGTCCCAGGC	85	346
5830	5849	502554	CCGTAGCTGCCTGTCCCAGG	83	347
5831	5850	502555	CCCGTAGCTGCCTGTCCCAG	64	348
5832	5851	502556	GCCCGTAGCTGCCTGTCCCA	83	349
5833	5852	502557	GGCCCGTAGCTGCCTGTCCC	89	350
5881	5900	502558	TAGAACATTTCATAGGCGAA	68	351
5919	5938	502559	TCTCCGCCGTGGAATCCGCG	75	352
5920	5939	502560	GTCTCCGCCGTGGAATCCGC	79	353
5921	5940	502561	GGTCTCCGCCGTGGAATCCG	66	354

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
5922	5941	502562	AGGTCTCCGCCGTGGAATCC	50	355
5923	5942	502563	TAGGTCTCCGCCGTGGAATC	71	356
5944	5963	502564	TTGTAGTGGACGATCTTGCC	68	357
5945	5964	502565	CTTGTAGTGGACGATCTTGC	70	358
5946	5965	502566	CCTTGTAGTGGACGATCTTG	61	359
5948	5967	503032	CACCTTGTAGTGGACGATCT	62	670
6039	6058	502582	CGGCAGAGAGAGGTGCTCCT	80	375
6040	6059	502583	GCGGCAGAGAGAGGTGCTCC	62	376
6041	6060	502584	AGCGGCAGAGAGAGGTGCTC	44	377
6042	6061	502585	CAGCGGCAGAGAGAGGTGCT	78	378
6043	6062	502586	CCAGCGGCAGAGAGAGGTGC	71	379
6118	6137	502587	GGCCCAGCCGTGTCTCCGGG	77	380
6119	6138	502588	CGGCCCAGCCGTGTCTCCGG	69	381
6120	6139	502589	CCGGCCCAGCCGTGTCTCCG	70	382
6121	6140	502590	CCCGGCCCAGCCGTGTCTCC	75	383
6122	6141	502591	CCCCGGCCCAGCCGTGTCTC	77	384
6123	6142	502592	ACCCCGGCCCAGCCGTGTCT	73	385
6124	6143	502593	CACCCCGGCCCAGCCGTGTC	84	386
6125	6144	502594	CCACCCCGGCCCAGCCGTGT	78	387
6126	6145	502595	TCCACCCCGGCCCAGCCGTG	71	388
6127	6146	502596	CTCCACCCCGGCCCAGCCGT	81	389
6128	6147	502597	GCTCCACCCCGGCCCAGCCG	86	390
6129	6148	502598	TGCTCCACCCCGGCCCAGCC	83	391
6130	6149	502599	CTGCTCCACCCCGGCCCAGC	88	392
6152	6171	502600	AAGGGATGTGTCCGGAAGTC	60	393
6153	6172	502601	GAAGGGATGTGTCCGGAAGT	58	394
6154	6173	502602	AGAAGGGATGTGTCCGGAAG	63	395
6155	6174	502603	AAGAAGGGATGTGTCCGGAA	62	396
6156	6175	502604	GAAGAAGGGATGTGTCCGGA	61	397
6157	6176	502605	AGAAGAAGGGATGTGTCCGG	62	398
6158	6177	502606	AAGAAGAAGGGATGTGTCCG	56	399
6159	6178	502607	AAAGAAGAAGGGATGTGTCC	58	400
6160	6179	502608	CAAAGAAGAAGGGATGTGTC	50	401
6161	6180	502609	CCAAAGAAGAAGGGATGTGT	61	402
6163	6182	502610	GGCCAAAGAAGAAGGGATGT	73	403
6164	6183	502611	AGGCCAAAGAAGAAGGGATG	56	404

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
6165	6184	502612	GAGGCCAAAGAAGAAGGGAT	73	405
6166	6185	502613	CGAGGCCAAAGAAGAAGGGA	75	406
6167	6186	502614	TCGAGGCCAAAGAAGAAGGG	75	407
6168	6187	502615	GTCGAGGCCAAAGAAGAAGG	83	408
6169	6188	502616	AGTCGAGGCCAAAGAAGAAG	58	409
6170	6189	502617	CAGTCGAGGCCAAAGAAGAA	52	410
6171	6190	502618	CCAGTCGAGGCCAAAGAAGA	68	411
6172	6191	502619	CCCAGTCGAGGCCAAAGAAG	78	412
6173	6192	502620	TCCCAGTCGAGGCCAAAGAA	66	413
6174	6193	502621	ATCCCAGTCGAGGCCAAAGA	75	414
6175	6194	502622	CATCCCAGTCGAGGCCAAAG	70	415
6176	6195	502623	CCATCCCAGTCGAGGCCAAA	81	416
6177	6196	502624	ACCATCCCAGTCGAGGCCAA	82	417
6178	6197	502625	GACCATCCCAGTCGAGGCCA	88	418
6179	6198	502626	AGACCATCCCAGTCGAGGCC	79	419
6180	6199	502627	GAGACCATCCCAGTCGAGGC	82	420
6181	6200	502628	GGAGACCATCCCAGTCGAGG	60	421
6216	6235	502629	TTCGAAATCCGGTGTAAAGG	84	422
6217	6236	502630	CTTCGAAATCCGGTGTAAAG	57	423
6218	6237	502631	CCTTCGAAATCCGGTGTAAA	64	424
6219	6238	502632	ACCTTCGAAATCCGGTGTAA	73	425
6220	6239	502633	CACCTTCGAAATCCGGTGTA	77	426
6221	6240	502634	GCACCTTCGAAATCCGGTGT	59	427
6222	6241	502635	GGCACCTTCGAAATCCGGTG	85	428
6223	6242	502636	TGGCACCTTCGAAATCCGGT	86	429
6224	6243	502637	GTGGCACCTTCGAAATCCGG	74	430
6225	6244	502638	GGTGGCACCTTCGAAATCCG	79	431
6226	6245	502639	CGGTGGCACCTTCGAAATCC	85	432
6227	6246	502640	TCGGTGGCACCTTCGAAATC	71	433
6228	6247	502641	GTCGGTGGCACCTTCGAAAT	88	434
6229	6248	502642	TGTCGGTGGCACCTTCGAAA	89	435
6230	6249	502643	GTGTCGGTGGCACCTTCGAA	88	436
6231	6250	502644	TGTGTCGGTGGCACCTTCGA	87	437
6232	6251	502645	ATGIGICGGTGGCACCTTCG	88	438
6233	6252	502646	CATGTGTCGGTGGCACCTTC	88	439

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
6234	6253	502647	GCATGTGTCGGTGGCACCTT	91	440
6235	6254	502648	TGCATGTGTCGGTGGCACCT	87	441
6236	6255	502649	TTGCATGTGTCGGTGGCACC	86	442
6237	6256	502650	GTTGCATGTGTCGGTGGCAC	83	443
6238	6257	502651	AGTTGCATGTGTCGGTGGCA	81	444
6239	6258	502652	AAGTTGCATGTGTCGGTGGC	79	445
6240	6259	502653	GAAGTTGCATGTGTCGGTGG	58	446
6241	6260	502654	CGAAGTTGCATGTGTCGGTG	85	447
6243	6262	502655	GTCGAAGTTGCATGTGTCGG	77	448
6244	6263	502656	AGTCGAAGTTGCATGTGTCG	79	449
6245	6264	502657	AAGTCGAAGTTGCATGTGTC	74	450
6246	6265	502658	CAAGTCGAAGTTGCATGTGT	82	451
6247	6266	502659	CCAAGTCGAAGTTGCATGTG	82	452
6248	6267	502660	ACCAAGTCGAAGTTGCATGT	70	453
6249	6268	502661	CACCAAGTCGAAGTTGCATG	76	454
6250	6269	502662	CCACCAAGTCGAAGTTGCAT	79	455
6251	6270	502663	TCCACCAAGTCGAAGTTGCA	68	456
6252	6271	502664	CTCCACCAAGTCGAAGTTGC	71	457
6253	6272	502665	CCTCCACCAAGTCGAAGTTG	67	458
6254	6273	502666	TCCTCCACCAAGTCGAAGTT	70	459
6255	6274	502667	GTCCTCCACCAAGTCGAAGT	80	460
6256	6275	502668	CGTCCTCCACCAAGTCGAAG	76	461
6257	6276	502669	CCGTCCTCCACCAAGTCGAA	78	462
6258	6277	502670	CCCGTCCTCCACCAAGTCGA	83	463
6259	6278	502671	GCCCGTCCTCCACCAAGTCG	76	464
6260	6279	502672	AGCCCGTCCTCCACCAAGTC	72	465
6261	6280	502673	GAGCCCGTCCTCCACCAAGT	71	466
6262	6281	502674	TGAGCCCGTCCTCCACCAAG	60	467
6289	6308	503033	CTACCCCGCCCCCGCTCACC	60	671
6445	6464	503034	CTAGGTCACTGCTGGGTCCT	86	672
6596	6615	503035	CTCAGATAGCTCCCCACTCC	55	673
6794	6813	503036	AATTCTCTAATTCTCTAGAC	19	674
8666	8685	503037	TACCTGAGGGCCATGCAGGA	51	675
8765	8784	503038	GTTCCAAGACTGATCCTGCA	69	676
11975	11994	502675	GGTTCCGAGCCTCTGCCTCG	44	468
11976	11995	502676	CGGTTCCGAGCCTCTGCCTC	74	469

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
11977	11996	502677	CCGGTTCCGAGCCTCTGCCT	72	470
11978	11997	502678	CCCGGTTCCGAGCCTCTGCC	73	471
11979	11998	502679	TCCCGGTTCCGAGCCTCTGC	84	472
11980	11999	502680	GTCCCGGTTCCGAGCCTCTG	66	473
11982	12001	502681	AGGTCCCGGTTCCGAGCCTC	82	474
11983	12002	502682	TAGGTCCCGGTTCCGAGCCT	83	475
11984	12003	502683	CTAGGTCCCGGTTCCGAGCC	81	476
11985	12004	502684	TCTAGGTCCCGGTTCCGAGC	74	477
11986	12005	502685	CTCTAGGTCCCGGTTCCGAG	78	478
11987	12006	502686	CCTCTAGGTCCCGGTTCCGA	75	479
11988	12007	502687	GCCTCTAGGTCCCGGTTCCG	80	480
12016	12035	502688	CATCCGCTCCTGCAACTGCC	89	481
12017	12036	502689	CCATCCGCTCCTGCAACTGC	81	482
12018	12037	502690	TCCATCCGCTCCTGCAACTG	71	483
12019	12038	502691	CTCCATCCGCTCCTGCAACT	75	484
12020	12039	502692	ACTCCATCCGCTCCTGCAAC	64	485
12021	12040	502693	AACTCCATCCGCTCCTGCAA	52	486
12022	12041	502694	CAACTCCATCCGCTCCTGCA	45	487
12024	12043	502695	AGCAACTCCATCCGCTCCTG	78	488
12025	12044	502696	CAGCAACTCCATCCGCTCCT	64	489
12026	12045	502697	GCAGCAACTCCATCCGCTCC	56	490
12173	12192	503039	AGGAGGGCGGTGGCGCGGCG	0	677
12221	12240	503040	TGACAGCTGGAAGGAGAAGA	41	678
12258	12277	502712	GAAGGTGGATCCGTGGCCCG	73	505
12259	12278	502713	GGAAGGTGGATCCGTGGCCC	70	506
12260	12279	502714	GGGAAGGTGGATCCGTGGCC	72	507
12261	12280	502715	TGGGAAGGTGGATCCGTGGC	50	508
12262	12281	502716	ATGGGAAGGTGGATCCGTGG	62	509
12263	12282	451417	CATGGGAAGGTGGATCCGTG	77	679
12463	12482	503041	GGAGGTTATCTAGGGAGATC	42	680
12542	12561	503042	GAAGGGACAGGTGACCCGAT	69	681
12596	12615	502724	CACCAGCGGGCACTGGCCCA	51	518
12597	12616	502725	CCACCAGCGGGCACTGGCCC	55	519
12598	12617	502726	CCCACCAGCGGGCACTGGCC	61	520
12599	12618	502727	CCCCACCAGCGGGCACTGGC	43	521

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
12601	12620	502728	GGCCCCACCAGCGGGCACTG	16	522
12602	12621	502729	TGGCCCCACCAGCGGGCACT	43	523
12603	12622	502730	CTGGCCCCACCAGCGGGCAC	43	524
12604	12623	502731	CCTGGCCCCACCAGCGGGCA	41	525
12605	12624	502732	GCCTGGCCCCACCAGCGGGC	30	526
12607	12626	502733	GGGCCTGGCCCCACCAGCGG	66	527
12625	12644	502734	AGGTGGCGGCGGTGCATGGG	31	528
12626	12645	502735	CAGGTGGCGGCGGTGCATGG	23	529
12627	12646	502736	GCAGGTGGCGGCGGTGCATG	57	530
12628	12647	502737	AGCAGGTGGCGGCGGTGCAT	54	531
12629	12648	502738	CAGCAGGTGGCGGCGGTGCA	61	532
12630	12649	502739	GCAGCAGGTGGCGGCGGTGC	57	533
12631	12650	502740	AGCAGCAGGTGGCGGCGGTG	36	534
12632	12651	502741	GAGCAGCAGGTGGCGGCGGT	53	535
12633	12652	502742	GGAGCAGCAGGTGGCGGCGG	39	536
12634	12653	502743	GGGAGCAGCAGGTGGCGGCG	36	537
12635	12654	502744	AGGGAGCAGCAGGTGGCGGC	62	538
12636	12655	502745	CAGGGAGCAGCAGGTGGCGG	56	539
12637	12656	502746	GCAGGGAGCAGCAGGTGGCG	58	540
12638	12657	502747	GGCAGGGAGCAGCAGGTGGC	65	541
12639	12658	502748	TGGCAGGGAGCAGCAGGTGG	47	542
12640	12659	502749	CTGGCAGGGAGCAGCAGGTG	41	543
12642	12661	451432	CCCTGGCAGGGAGCAGCAGG	53	544
12643	12662	502750	ACCCTGGCAGGGAGCAGCAG	52	545
12646	12665	503043	CGTACCCTGGCAGGGAGCAG	59	682
12918	12937	502977	GGACTCGCCCCGCCTACGCC	71	683
12924	12943	502978	CTCCTGGGACTCGCCCCGCC	67	684
12925	12944	503044	GCTCCTGGGACTCGCCCCGC	66	685
12929	12948	503045	ATTGGCTCCTGGGACTCGCC	77	686
12930	12949	502979	GATTGGCTCCTGGGACTCGC	70	687
12936	12955	502980	GCCTCTGATTGGCTCCTGGG	56	688
12942	12961	502981	GCATGGGCCTCTGATTGGCT	20	689
12948	12967	502982	CACCCGGCATGGGCCTCTGA	20	690
12986	13005	503046	GCCAGGCCTAGGGACCTGCG	58	691
12990	13009	502760	ATAGGCCAGGCCTAGGGACC	51	555
12991	13010	502761	GATAGGCCAGGCCTAGGGAC	41	556

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
12992	13011	502762	CGATAGGCCAGGCCTAGGGA	69	557
12993	13012	502763	CCGATAGGCCAGGCCTAGGG	80	558
12994	13013	502764	TCCGATAGGCCAGGCCTAGG	78	559
12995	13014	502765	CTCCGATAGGCCAGGCCTAG	89	560
12996	13015	502766	CCTCCGATAGGCCAGGCCTA	79	561
12997	13016	502767	GCCTCCGATAGGCCAGGCCT	73	562
12999	13018	502768	GCGCCTCCGATAGGCCAGGC	83	563
13015	13034	502769	AACAGGAGCAGGGAAAGCGC	83	564
13016	13035	502770	GAACAGGAGCAGGGAAAGCG	70	565
13017	13036	502771	CGAACAGGAGCAGGGAAAGC	43	566
13018	13037	502772	GCGAACAGGAGCAGGGAAAG	47	567
13019	13038	502773	GGCGAACAGGAGCAGGGAAA	61	568
13020	13039	502774	CGGCGAACAGGAGCAGGGAA	74	569
13021	13040	502775	ACGGCGAACAGGAGCAGGGA	60	570
13022	13041	502776	AACGGCGAACAGGAGCAGGG	86	571
13023	13042	502777	CAACGGCGAACAGGAGCAGG	84	572
13044	13063	502778	GGGCGGCGGCACGAGACAGA	80	573
13045	13064	502779	AGGGCGGCGGCACGAGACAG	76	574
13046	13065	502780	CAGGGCGGCGGCACGAGACA	58	575
13047	13066	502781	CCAGGGCGGCGGCACGAGAC	80	576
13048	13067	502782	CCCAGGGCGGCGGCACGAGA	59	577
13049	13068	502783	GCCCAGGGCGGCGGCACGAG	68	578
13050	13069	502784	AGCCCAGGGCGGCGGCACGA	75	579
13051	13070	502785	CAGCCCAGGGCGGCGGCACG	76	580
13052	13071	502786	GCAGCCCAGGGCGGCGGCAC	70	581
13089	13108	502787	CTGCGGTGAGTTGGCCGGCG	68	582
13090	13109	502788	ACTGCGGTGAGTTGGCCGGC	67	583
13091	13110	502789	GACTGCGGTGAGTTGGCCGG	58	584
13092	13111	502790	AGACTGCGGTGAGTTGGCCG	71	585
13093	13112	502791	CAGACTGCGGTGAGTTGGCC	70	586
13094	13113	502792	CCAGACTGCGGTGAGTTGGC	79	587
13095	13114	502793	GCCAGACTGCGGTGAGTTGG	76	588
13096	13115	502794	CGCCAGACTGCGGTGAGTTG	66	589
13140	13159	502795	AAGACAGTTCTAGGGTTCAG	87	590
13141	13160	502796	GAAGACAGTTCTAGGGTTCA	78	591

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
13142	13161	502797	CGAAGACAGTTCTAGGGTTC	85	592
13143	13162	502798	TCGAAGACAGTTCTAGGGTT	78	593
13144	13163	502799	GTCGAAGACAGTTCTAGGGT	92	594
13145	13164	502800	AGTCGAAGACAGTTCTAGGG	85	595
13146	13165	502801	GAGTCGAAGACAGTTCTAGG	83	596
13147	13166	502802	GGAGTCGAAGACAGTTCTAG	86	597
13148	13167	502803	CGGAGTCGAAGACAGTTCTA	91	598
13149	13168	502804	CCGGAGTCGAAGACAGTTCT	76	599
13150	13169	502805	CCCGGAGTCGAAGACAGTTC	90	600
13151	13170	502806	CCCCGGAGTCGAAGACAGTT	83	601
13152	13171	502807	GCCCCGGAGTCGAAGACAGT	82	602
13153	13172	502808	GGCCCCGGAGTCGAAGACAG	73	603
13154	13173	502809	GGGCCCCGGAGTCGAAGACA	67	604
13206	13225	502810	AGGCGGTGGGCGCGGCTTCT	73	605
13207	13226	502811	CAGGCGGTGGGCGCGGCTTC	57	606
13208	13227	502812	GCAGGCGGTGGGCGCGGCTT	69	607
13210	13229	502813	TGGCAGGCGGTGGGCGCGGC	73	608
13212	13231	502814	ACTGGCAGGCGGTGGGCGCG	56	609
13214	13233	502815	GAACTGGCAGGCGGTGGGCG	71	610
13215	13234	502816	TGAACTGGCAGGCGGTGGGC	80	611
13217	13236	502817	TGTGAACTGGCAGGCGGTGG	85	612
13250	13269	502818	TGGAGCTGGGCGGAGACCCA	55	613
13252	13271	502819	ACTGGAGCTGGGCGGAGACC	53	614
13253	13272	502820	GACTGGAGCTGGGCGGAGAC	55	615
13255	13274	502821	AGGACTGGAGCTGGGCGGAG	76	616
13257	13276	502822	ACAGGACTGGAGCTGGGCGG	77	617
13258	13277	502823	CACAGGACTGGAGCTGGGCG	74	618
13259	13278	502824	TCACAGGACTGGAGCTGGGC	90	619
13449	13468	502825	GCCTCAGCCTGGCCGAAAGA	80	620
13450	13469	502826	GGCCTCAGCCTGGCCGAAAG	72	621
13553	13572	444401	TTGCACTTTGCGAACCAACG	97	41
14037	14056	503047	TTCCTCCCCCAACCCTGATT	34	692
14255	14274	503048	AAGTTTGCAGCAACTTTTCT	0	693
14325	14344	503049	GCCCCTCGGAATTCCCGGCT	0	694
14343	14362	503050	CATCTCGGCCTGCGCTCCGC	39	695

TABLE 13-continued

Inhibition of human DMPK RNA transcript in hSKMc by 5-10-5 gapmers targeting SEQ ID NO: 2

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
14361	14380	503051	GCAGGCCCCCACATTCCCCA	0	696
14392	14411	503052	CTTCTGCACGCCTCCGTCTC	30	697

Example 8

Antisense Inhibition of Murine DMPK in Mouse Primary Hepatocytes

[0338] Antisense oligonucleotides targeted to a murine DMPK nucleic acid were tested for their effect on DMPK RNA transcript in vitro. Cultured mouse primary hepatocytes at a density of 35,000 cells per well were transfected using electroporation with 8,000 nM antisense oligonucleotide. After approximately 24 hours, RNA was isolated from the cells and DMPK transcript levels were measured by quantitative real-time PCR. DMPK RNA transcript levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of DMPK, relative to untreated control cells.

[0339] The antisense oligonucleotides in Tables 14, 15, and 16 are 5-10-5 gapmers, where the gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises five 2'-MOE nucleosides. The internucleoside linkages throughout each gapmer are phosphorothioate (P═S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. 'Murine Target start site' indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted in the murine gene sequence. 'Murine Target stop site' indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted in the murine gene sequence. All the antisense oligonucleotides listed in Table 12 target SEQ ID NO: 3 (GENBANK Accession No. NT_039413.7 truncated from nucleotides 16666001 to 16681000). All the antisense oligonucleotides listed in Table 13 target SEQ ID NO: 4 (GENBANK Accession No. NM_032418.1). The antisense oligonucleotides of Table 14 target SEQ ID NO: 5 (GENBANK Accession No. AI007148.1), SEQ ID NO: 6 (GENBANK Accession No. AI304033.1), SEQ ID NO: 7 (GENBANK Accession No. BC024150.1), SEQ ID NO: 8 (GENBANK Accession No. BC056615.1), SEQ ID NO: 793 (GENBANK Accession No. BC075715.1), SEQ ID NO: 794 (GENBANK Accession No. BU519245.1), SEQ ID NO: 795 (GENBANK Accession No. CB247909.1), SEQ ID NO: 796 (GENBANK Accession No. CX208906.1), SEQ ID NO: 797 (GENBANK Accession No. CX732022.1), SEQ ID NO: 798 (GENBANK Accession No. S60315.1), or SEQ ID NO: 799 (GENBANK Accession No. S60316.1). In addition, the human antisense oligonucleotide ISIS 451421 targeting SEQ ID NO: 800 (GENBANK Accession No. NM_001081562.1) was also included in this assay and is listed in Table 14.

[0340] The murine oligonucleotides of Tables 14, 15, and 16 may also be cross-reactive with human gene sequences. 'Mismatches' indicate the number of nucleobases by which the murine oligonucleotide is mismatched with a human gene sequence. The greater the complementarity between the murine oligonucleotide and the human sequence, the more likely the murine oligonucleotide can cross-react with the human sequence. The murine oligonucleotides in Tables 14, 15, and 16 were compared to SEQ ID NO: 800 (GENBANK Accession No. NM_001081562.1). "Human Target start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Human Target stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence.

[0341] Several of the tested antisense oligonucleotides demonstrated significant inhibition of DMPK mRNA levels under the conditions specified above. Certain of the tested antisense oligonucleotides are cross-reactive with human gene sequences.

TABLE 14

Inhibition of murine DMPK RNA transcript in mouse primary hepatocytes by 5-10-5 gapmers targeting SEQ ID NO: 800

Murine Target Start Site	Murine Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.	Human Target Start Site	Human Target Stop Site	Mismatches
11904	11923	299516	TGGCCCACAGCCACGGCCGG	47	698	1850	1869	0
11927	11946	299520	GGCCTGGCCCCACCAGCGGG	58	699	1873	1892	0
11962	11981	299521	CCTGGCAGGGAGCAGCAGGT	44	700	1908	1927	0
3345	3364	451360	CAGCCGCACTTCGGCTGACA	29	701	207	226	1
3378	3397	451361	GCCTGGGTCCAGCACCAGCT	67	702	240	259	2
3388	3407	451362	GTCCCAGGAAGCCTGGGTCC	62	703	250	269	2

TABLE 14-continued

Inhibition of murine DMPK RNA transcript in mouse primary hepatocytes by 5-10-5 gapmers targeting SEQ ID NO: 800

Murine Target Start Site	Murine Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.	Human Target Start Site	Human Target Stop Site	Mismatches
3418	3437	451363	CGCCCAGGAGAAGGTCGAGC	69	213	280	299	0
3484	3503	451364	CCCACTGCAAGAAGTCGGCC	69	226	346	365	0
6264	6283	451366	CGTTAGCAGGTCCCCGCCCA	73	704	660	679	2
6342	6361	451367	GTCTATGGCCATGACAATCT	61	705	738	757	0
6363	6382	451368	GTAGCCCAGCCGGTGCACGG	54	706	759	778	2
6851	6870	451370	GGGTGCCCACAGCCACCAGC	72	707	889	908	0
6919	6938	451371	TGGCCCGTAGCTGCCTGCCC	80	708	957	976	2
7448	7467	451373	GGAAATCACCTGCCCCACCT	80	709	n/a	n/a	n/a
7458	7477	451374	GGATGTTTCTGGAAATCACC	84	710	n/a	n/a	n/a
7533	7552	451375	GTGGCACCCTCGAAGTCTGG	77	711	1271	1290	3
7589	7608	451376	CCCCGCTCACCATGGCAGTG	31	712	n/a	n/a	n/a
10278	10297	451378	GGTCCGGGACCTGATTGTCT	85	713	n/a	n/a	n/a
3229	3248	451385	GCTGCATGTCTGCCCGTCCC	74	714	90	109	1
3244	3263	451386	GGCCCCAGAACCCTAGCTGC	73	715	n/a	n/a	n/a
3270	3289	451387	TCACAGGGCCTGGCTGCCCC	62	716	131	150	1
3333	3352	451388	GGCTGACATGTTGGGCAGGC	60	717	195	214	1
3250	3269	451389	TGTCCAGGCCCCAGAACCCT	68	718	111	130	3
12295	12314	451391	GGCCAGGCCTAGGGATCTGC	51	719	n/a	n/a	n/a
12306	12325	451392	CGCCTCGGATAGGCCAGGCC	52	720	1935	1954	1
12450	12469	451393	GGCTTGGAGTCTTAGGGTTC	85	721	n/a	n/a	n/a
12623	12642	451394	TCCCCGGCCGCCAGGTGGCA	43	722	2224	2243	3
12651	12670	451395	GGTGCTGGGCACGAGCCCTG	62	723	n/a	n/a	n/a
12698	12717	451396	GCCCAGCTGCTGCAGCAGCG	66	724	n/a	n/a	n/a
12876	12895	451397	CCGTGTGTGCTGGCAGAGGT	76	725	n/a	n/a	n/a
13084	13103	451398	ATAAATACCGAGGAATGTCG	77	726	2766	2785	0
13094	13113	451399	GGGACAGACAATAAATACCG	80	727	2776	2795	0
12362	12381	451405	GTGCAGCCCAGTGTGGCGGC	69	728	1991	2010	3
11175	11194	451415	CCTGGAGAAGTTCTGGTTGG	48	729	1674	1693	3
11585	11604	451417	CATGGGAAGGTGGATCCGTG	65	679	1819	1838	1
11854	11873	451419	GGTGACCCGATCGGAGCCCA	11	730	n/a	n/a	n/a
11874	11893	451420	AGCTGGAGAGAGAAGGGACA	37	731	n/a	n/a	n/a
11379	11398	451422	GTGAGGGACTCGCCTGCGGC	36	732	n/a	n/a	n/a
11479	11498	451423	GCGGCTGCGGTGCCCCAGCC	50	733	n/a	n/a	n/a
11883	11902	451424	GGGCCATCTAGCTGGAGAGA	45	734	n/a	n/a	n/a
3485	3504	451427	CCCCACTGCAAGAAGTCGGC	57	735	347	366	1

TABLE 14-continued

Inhibition of murine DMPK RNA transcript in mouse primary hepatocytes by 5-10-5 gapmers targeting SEQ ID NO: 800

Murine Target Start Site	Murine Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.	Human Target Start Site	Human Target Stop Site	Mismatches
4621	4640	451428	TTGAGCCCTTTTAAGGCAGC	43	736	n/a	n/a	n/a
6232	6251	451429	TGACCAGGTACTGGGAGCGG	47	737	n/a	n/a	n/a
10985	11004	451430	CCTGGAGCTGGATCAGTCCC	6	738	n/a	n/a	n/a
11586	11605	451431	ACATGGGAAGGTGGATCCGT	70	739	1820	1839	1
11963	11982	451432	CCCTGGCAGGGAGCAGCAGG	42	544	1909	1928	0
11973	11992	451433	GTGGGACATACCCTGGCAGG	34	740	n/a	n/a	n/a
12294	12313	451434	GCCAGGCCTAGGGATCTGCA	35	741	n/a	n/a	n/a

TABLE 15

Inhibition of murine DMPK RNA transcript in mouse primary hepatocytes by 5-10-5 gapmers targeting SEQ ID NO: 800

Murine Target Start Site	Murine Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.	Human Target Start Site	Human Target Stop Site	Mismatches
330	349	451365	GGAAGCACGACACCTCGCCT	67	742	535	554	1
662	681	451369	CCTCACCATTCCATCAGGCT	81	743	n/a	n/a	n/a
881	900	451372	CGGCAGCGACAAGTGTTCCC	90	744	n/a	n/a	n/a
1217	1236	451377	GTCTCTGAAGGCCATGCAGC	69	745	1407	1426	3
1329	1348	451379	CAGCCACTTGATCCGGTGGG	62	746	n/a	n/a	n/a
1342	1361	451380	AGGTCGGCCTCTTCAGCCAC	74	747	n/a	n/a	n/a
1494	1513	451381	GTTGGCTGGAGAAGTTCTGG	39	748	1678	1697	2
1598	1617	451382	CCCCGTGATGGCTGCGGCTC	54	749	1782	1801	3
1644	1663	451383	GGCCATCTAGATGGGAAGGT	21	517	1828	1847	0
1741	1760	451384	AGGCCAGGCCTAGGGATCCT	39	750	1925	1944	1

TABLE 16

Inhibition of murine DMPK RNA transcript in mouse primary hepatocytes by 5-10-5 gapmers targeting SEQ ID NOs: 5-8 and 793-799

Murine Target Start Site	Murine Target Stop Site	Murine Target SEQ ID NO	ISIS No	Sequence	% inhibition	SEQ ID NO.	Human Target Start Site	Human Target Stop Site	Mismatches
324	343	5	451410	GGCGCGGTGCCCCAGCCTGG	67	751	n/a	n/a	n/a
485	504	5	451411	GTCCTGGCCCCACCAGCGGG	66	752	1873	1892	1
534	553	5	451412	CCAGGCCTAGGAATCCTGGC	17	753	1922	1941	2
547	566	5	451413	GCGCCTCGGATAGCCAGGCC	51	754	n/a	n/a	n/a
594	613	5	451414	CCCAGTGTGGCGCAGCAGCC	65	755	n/a	n/a	n/a

TABLE 16-continued

Inhibition of murine DMPK RNA transcript in mouse primary hepatocytes by 5-10-5 gapmers targeting SEQ ID NOs: 5-8 and 793-799

Murine Target Start Site	Murine Target Stop Site	Murine Target SEQ ID NO	ISIS No	Sequence	% inhibition	SEQ ID NO.	Human Target Start Site	Human Target Stop Site	Mismatches
393	412	6	451402	GTGTTTCATCTTCACCACCG	80	756	462	481	3
1475	1494	7	451390	AGGTCAGCCTCTTCAGCCAC	60	757	n/a	n/a	n/a
n/a	n/a	n/a	451425	GGCCATATGGGAAGGTGGAT	48	758	1824	1843	0
1763	1782	8	451418	GGAGGATTTGGCGAGAAGCA	48	759	n/a	n/a	n/a
1032	1051	793	451403	CGAAGTCTGCCCCACCTCGA	58	760	n/a	n/a	n/a
1042	1061	793	451404	GTGGCACCCTCGAAGTCTGC	72	761	n/a	n/a	n/a
217	236	794	451400	GGGTCCATTGTAAGGAAGCT	4	762	n/a	n/a	n/a
754	773	794	451401	GGTGCCCACAGCCACCAGGG	82	763	888	907	1
322	341	795	451406	TCCATGGCAGTGAGCCGGTC	55	764	1319	1338	1
523	542	795	451407	GGGACCACTTGATCCGGTGG	63	765	n/a	n/a	n/a
534	553	795	451408	GGATCAGAGTTGGGACCACT	0	766	n/a	n/a	n/a
492	511	796	451416	CCCCGTGATGGCTGCGGTTC	49	767	n/a	n/a	n/a
469	488	797	451409	GTGTGTCCTCATACCCCGCC	60	768	n/a	n/a	n/a
629	648	798	451421	GCACCCTCGAAGTCTCGACC	72	769	n/a	n/a	n/a
854	873	799	451426	GCTCTGAAGGCCATGCAGCA	52	770	n/a	n/a	n/a

Example 9

Dose-Dependent Antisense Inhibition of Murine DMPK in Mouse Primary Hepatocytes

[0342] Several of the antisense oligonucleotides exhibiting in vitro inhibition of DMPK in mouse primary hepatocytes (see Example 8) were tested at various doses. Cells were plated at a density of 35,000 cells per well and transfected using electroporation with 1,000 nM, 2,000 nM, 4,000 nM, 8,000 nM, and 16,000 nM concentrations of each antisense oligonucleotide. After approximately 16 hours, RNA was isolated from the cells and DMPK transcript levels were measured by quantitative real-time PCR using primer probe set RTS3181 (forward sequence GACATATGCCAAGATTGTGCACTAC, designated herein as SEQ ID NO: 771; reverse sequence CACGAATGAGGTCCTGAGCTT, designated herein as SEQ ID NO: 772; probe sequence AACACTTGTCGCTGCCGCTGGCX, designated herein as SEQ ID NO: 773). DMPK transcript levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in Table 17 as percent inhibition of DMPK, relative to untreated control cells.

[0343] The majority of the tested antisense oligonucleotides demonstrated dose-dependent inhibition of DMPK mRNA levels under the conditions specified above.

TABLE 17

Dose-dependent antisense inhibition of murine DMPK in mouse primary hepatocytes

ISIS No	1,000 nM	2,000 nM	4,000 nM	8,000 nM	16,000 nM	IC_{50} (μM)
451369	33	59	78	87	94	1.57
451371	60	77	84	90	91	0.24
451373	53	62	82	89	92	0.74
451374	33	42	76	88	94	2.00
451375	43	62	81	89	88	1.05
451378	39	79	80	87	94	0.87
451385	22	57	80	78	93	2.01
451393	49	63	86	80	80	0.59
451397	63	75	74	81	92	0.22
451398	29	72	84	83	90	1.29
451399	27	53	81	68	80	2.07
451401	34	71	87	86	92	1.12
451402	34	69	75	86	74	1.14

Example 10

Antisense Inhibition of Human Alpha1 Skeletal Actin in HepG2 Cells

[0344] Antisense oligonucleotides targeted to a human alpha1 skeletal actin nucleic acid, a gene which may carry an expanded CTG repeat capable of causing symptoms of DM1 when inserted into mouse models, were tested for their effect on alpha1 actin RNA transcript in vitro. Cultured HepG2 cells at a density of 20,000 cells per well were transfected using

electroporation with 10,000 nM antisense oligonucleotide. After approximately 24 hours, RNA was isolated from the cells and alpha1 actin RNA transcript levels were measured by quantitative real-time PCR. Alpha1 actin RNA transcript levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of alpha1 actin, relative to untreated control cells.

[0345] The antisense oligonucleotides in Table 18 are 5-10-5 gapmers, where the gap segment comprises ten 2'-deoxynucleosides and each wing segment comprises five 2'-MOE nucleosides. The internucleoside linkages throughout each gapmer are phosphorothioate (P═S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. 'Target start site' indicates the 5'-most nucleoside to which the antisense oligonucleotide is targeted. 'Target stop site' indicates the 3'-most nucleoside to which the antisense oligonucleotide is targeted. All the antisense oligonucleotides listed in Table 18 target SEQ ID NO: 801 (GENBANK Accession No. NM_001100.3).

[0346] The tested antisense oligonucleotide sequences demonstrated dose-dependent inhibition of alpha 1 actin mRNA levels under the conditions specified above.

TABLE 18

Inhibition of human alpha1 actin RNA transcript in HepG2 cells by 5-10-5 gapmers targeting SEQ ID NO: 801

Target Start Site	Target Stop Site	ISIS No	Sequence	% inhibition	SEQ ID NO.
16	35	445205	AGCGAGGCTTCACTTGGCGC	74	774
20	39	190403	GGGAAGCGAGGCTTCACTTG	75	775
1028	1047	190401	GCGGTCAGCGATCCCAGGGT	78	776
1058	1077	445225	GGGTGCCAGCGCGGTGATCT	73	777
1320	1339	445231	TGTTACAAAGAAAGTGACTG	74	778
1339	1358	445232	CGATGGCAGCAACGGAAGTT	96	779
1348	1367	445233	GTCAGTTTACGATGGCAGCA	100	780
1417	1436	445235	CAGGGCTTTGTTTCGAAAAA	91	781
1430	1449	445236	CCATTTTCTTCCACAGGGCT	99	782
1447	1466	445237	ATGCTTCTTCAAGTTTTCCA	97	783
1460	1479	445238	CAGAATGACTTTAATGCTTC	95	784

Example 11

Dose-Dependent Antisense Inhibition of Human Alpha1 Actin in HepG2 Cells

[0347] Several of the antisense oligonucleotides exhibiting in vitro inhibition of alpha1 actin in HepG2 cells (see Example 8) were tested at various doses. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 625 nM, 1,250 nM, 2,500 nM, 5,000 nM, 10,000 nM and 20,000 nM concentrations of each antisense oligonucleotide. After approximately 16 hours, RNA was isolated from the cells and alpha1 actin RNA transcript levels were measured by quantitative real-time PCR using primer probe set RTS3154 (forward sequence CCACCGCAAATGCTTCTAGAC, designated herein as SEQ ID NO: 785; reverse sequence CCCCCCCATTGAGAAGATTC, designated herein as SEQ ID NO: 786; probe sequence CTCCACCTCCAGCACGCGACTTCTX, designated herein as SEQ ID NO: 787). Alpha1 actin RNA transcript levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented in Table 19 as percent inhibition of alpha1 actin, relative to untreated control cells.

[0348] Several of the antisense oligonucleotides demonstrated dose-dependent inhibition of alpha 1 actin mRNA levels under the conditions specified above.

TABLE 19

Dose-dependent antisense inhibition of human alpha1 actin in HepG2 cells

ISIS No.	625 nM	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
445233	21	72	63	82	96	83	1.1
445236	26	68	82	91	90	91	0.8
445237	36	59	76	84	83	90	0.8
445232	14	42	54	59	80	91	2.6

TABLE 19-continued

Dose-dependent antisense inhibition of human alpha1 actin in HepG2 cells

ISIS No.	625 nM	1,250 nM	2,500 nM	5,000 nM	10,000 nM	20,000 nM	IC_{50} (μM)
445238	27	43	54	73	76	90	2.0
445235	26	52	29	58	59	24	0.7
190403	25	29	36	25	61	54	11.9
190401	17	14	40	68	76	72	3.9
445225	25	23	49	28	52	50	15.8
445205	26	31	34	28	55	36	7.6
445231	30	25	39	26	42	36	>20.0

Example 12

In Vivo Antisense Inhibition of Human Alpha1 Actin by Intramuscular Administration in Transgenic Mice

[0349] To test the effect of antisense inhibition for the treatment of myotonic dystrophy, an appropriate mouse model was required. The HSA^{LR} mouse model is an established model for DM1 (Mankodi, A. et al. Science. 289: 1769, 2000). The mice carry a human skeletal actin (hACTA1) transgene with 220 CTG repeats inserted in the 3' UTR of the gene. The hACTA1-CUGexp transcript accumulates in nuclear foci in skeletal muscles and results in myotonia similar to that in human DM1 (Mankodi, A. et al. Mol. Cell 10: 35, 2002; Lin, X. et al. Hum. Mol. Genet. 15: 2087, 2006). Hence, it was expected that amelioration of DM1 symptoms in the HSA^{LR} mouse by antisense inhibition of the hACTA1 transgene would predict amelioration of similar symptoms in human patients by antisense inhibition of the DMPK transcript.

[0350] HSA (human skeletal actin)^{LR} (long repeat) DM1 mice were generated by insertion in FVB/N mice of a transgene with 250 CUG repeats in the 3' UTR of human skeletal actin. The transgene is expressed in the mice as a CUG repeat RNA, which is retained in the nucleus, forming nuclear inclusions or foci, similar to that seen in human tissue samples of patients with myotonic dystrophy (DM1).

[0351] ISIS 190403 and ISIS 445238, which demonstrated statistically significant dose-dependent inhibition in vitro (see Example 11), were evaluated for their ability to reduce human alpha1 actin RNA transcript in vivo.

Treatment

[0352] HSA^{LR} mice were maintained on a 12-hour light/dark cycle and fed ad libitum normal Purina mouse chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. Antisense oligonucleotides (ASOs) were prepared in PBS and sterilized by filtering through a 0.2 micron filter. Oligonucleotides were dissolved in 0.9% PBS for injection.

[0353] The mice were divided into two treatment groups. The two groups received direct intramuscular injections of ISIS 190403 or ISIS 445238 at a dose of 0.8 nM into the tibialis anterior muscle on one side. The contralateral tibialis anterior muscle in each mouse received a single dose intramuscular injection of PBS. The PBS-injected muscle acted as the control.

Inhibition of Alpha1 Actin RNA

[0354] Twenty four hours after the final dose, the animals were sacrificed and tissue from the tibialis anterior muscles of both sides was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 20, treatment with antisense oligonucleotides reduced human alpha1 actin RNA transcript expression. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

[0355] The results indicate that treatment with ISIS 190403 and ISIS 445238 resulted in inhibition of alpha 1 actin RNA levels in the mice.

TABLE 20

Percent inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

ISIS No.	% inhibition
190403	38
445238	40

Example 13

Dose Dependent Antisense Inhibition of Human Alpha1 Actin by Intramuscular Administration in Transgenic Mice

[0356] ISIS 445236, which demonstrated statistically significant dose-dependent inhibition in vitro (see Example 11), was evaluated for its ability to reduce human alpha1 actin RNA transcript in vivo.

Treatment

[0357] HSA^{LR} mice were maintained on a 12-hour light/dark cycle and fed ad libitum normal Purina mouse chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. Antisense oligonucleotides (ASOs) were prepared in PBS and sterilized by filtering through a 0.2 micron filter. Oligonucleotides were dissolved in 0.9% PBS for injection.

[0358] The mice were divided into three treatment groups. The groups received direct intramuscular injections of ISIS 445236 at doses of 0.2 nM, 0.4 nM or 0.8 nM into the tibialis anterior muscle of one side. The contralateral tibialis anterior muscle in each mouse received a single dose intramuscular injection of PBS. The PBS-injected muscle acted as the control.

Inhibition of Alpha1 Actin RNA

[0359] Twenty four hours after the final dose, the animals were sacrificed and tissue from the tibialis anterior muscles of both sides was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 21, treatment with ISIS 445236 reduced human alpha1 actin RNA transcript expression at all dosages. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the control.

[0360] The results indicate that treatment with ISIS 445236 resulted in significant inhibition of alpha 1 actin mRNA levels under the conditions specified above.

TABLE 21

Inhibition of human alpha1 actin RNA transcript by ISIS 445236 in HSA^{LR} mice

Dose (nM)	% inhibition
0.2	70
0.4	54
0.8	78

Assessment of Myotonia by Electromyography

[0361] Myotonia refers to repetitive action potential that is due to delayed relaxation of muscle fibers. This phenomenon is observed in patients of myotonic dystrophy as well as in the HSA^{LR} mice. When the EMG needle is inserted into a myotonic muscle, the electrical activity is prolonged for up to several seconds past when the insertional activity should normally cease. The frequency of myotonic discharges ranges from 50 to 100 impulses per second.

[0362] Myotonia was measured via electromyography and graded in the following manner: grade 0 refers to no myotonia elicited by any needle insertion (0%); grade 1 refers to myotonia elicited by less than 50% needle insertions; grade 2 refers to myotonia elicited by more than 50% needle insertions; and grade 3 refers to mytonia elicited by 100% needle insertions.

[0363] Before electromyography, mice were anesthetized by using i.p. a cocktail of 100 mg/kg ketamine, 10 mg/kg xylazine, and 3 mg/kg acepromazine. Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 22 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with ISIS 445236.

TABLE 22

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

Treatment	Dose (nM)	Myotonia grade
PBS		2.7
ISIS 455236	0.2	1.3
	0.4	1.0
	0.8	1.0

Correction of Alternative Splicing

[0364] In DM1/HSA^{LR} mouse model, the accumulation of expanded CUG RNA in the nucleus leads to the sequestration of poly(CUG)-binding proteins, such as Muscleblind-like 1 (MBLN1) (Miller, J. W. et al. EMBO J. 19: 4439, 2000). The splicing factor MBNL1, which controls alternative splicing of the Serca1 gene is sequestered in expanded CUG foci. This triggers dysregulation of the alternative splicing of this gene. To evaluate the effect of antisense inhibition of human alpha 1 actin on such alternative splicing, total RNA was purified from the tibialis anterior, gastrocnemius, and quadriceps muscle using RNeasy Lipid Tissue Mini Kit (Qiagen), according to the manufacturer's instructions. RT-PCR was performed with the SuperScript III One-Step RT-PCR System and Platinum Taq Polymerase (Invitrogen), using gene-specific primers for cDNA synthesis and PCR amplification. The forward and reverse primers for Serca-1 have been described in Bennett and Swayze (Annu. Rev. Pharmacol. 2010; 50: 259-93). PCR products were separated on agarose gels, stained with SybrGreen I Nucleic Acid Gel Stain (Invitrogen), and imaged using a Fujifilm LAS-3000 Intelligent Dark Box.

[0365] The PCR products of Serca1 splicing in the PBS control demonstrated exon 22 exclusion as a result of dysregulation of MBLN1. Treatment with ISIS 445236 resulted in exon 22 inclusion and normalization of alternative splicing of the Serca1 gene in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0366] Therefore, antisense inhibition of alpha1 actin corrected Serca1 splicing dysregulation, which indicates that treatment with antisense oligonucleotide reduced accumulation of CUGexp in the nuclear foci. Reduced accumulation of CUGexp in the nuclear foci corrects MBLN1 sequestration thereby allowing normal splicing to occur.

Example 14

In Vivo Antisense Inhibition of Human Alpha1 Actin by Subcutaneous Administration in Transgenic Mice

[0367] ISIS 190403, ISIS 445236 and ISIS 445238 were evaluated for their ability to reduce human alpha1 actin RNA transcript in vivo.

Treatment

[0368] HSA^{LR} mice were maintained on a 12-hour light/dark cycle and fed ad libitum normal Purina mouse chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. Antisense oligonucleotides (ASOs) were prepared in PBS and sterilized by filtering through a 0.2 micron filter. Oligonucleotides were dissolved in 0.9% PBS for injection.

[0369] The mice were divided into four treatment groups. The first three groups received subcutaneous injections of ISIS 190403, ISIS 445236 or ISIS 445238 at a dose of 25 mg/kg twice per week for 4 weeks. The fourth group received subcutaneous injections of PBS twice weekly for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Inhibition of Alpha1 Actin RNA

[0370] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles (left and right), gastrocnemius muscles (left and right), and tibialis anterior muscles (left and right) was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 23, treatment with antisense oligonucleotides reduced human alpha1 actin RNA transcript expression. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the control.

[0371] Both ISIS 445236 and ISIS 445238 demonstrated significant inhibition of alpha1 actin mRNA levels under the conditions specified above.

TABLE 23

Percent inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

Muscle Type	ISIS 190403	ISIS 445236	ISIS 445238
Quadriceps	16	83	72
Gastrocnemius	0	85	73
Tibialis anterior	2	81	71

Fluorescence In Situ Hybridization of Alpha1 Actin in Muscles

[0372] Frozen muscle tissue sections were fixed in fresh 3% paraformaldehyde in PBS solution for 15-20 minutes, after which they were rinsed twice with PBS for 5 minutes. The nuclei were permeabilized with 0.5% Triton X-100 for 5 minutes after which the tissue was blocked with normal goat serum for 30 minutes. The sections were incubated a 2'-O-methyl RNA targeted to alpha1 actin that is 5'-labeled with Texas Red (Integrated DNA Technologies). The sections were counter-stained with DAPI to label the nuclei. The sections were mounted and viewed with a standard fluorescence microscope. Image acquisition was by Metavue software and deconvolution was achieved by Autoquant software.

[0373] All muscle tissue sections from mice treated with ISIS 445236 and ISIS 445238 displayed reduced fluorescent intensity of alpha1 actin signal at the ribonuclear foci, indicating antisense inhibition of human alpha1 actin mRNA and reduction of the RNA in the nuclear foci.

Assessment of Myotonia by Electromyography

[0374] Myotonia refers to repetitive action potential that is due to delayed relaxation of muscle fibers. This phenomenon is observed in patients of myotonic dystrophy as well as in the HSA^{LR} mice. When the EMG needle is inserted into a myotonic muscle, the electrical activity is prolonged for up to several seconds past when the insertional activity should normally cease. The frequency of myotonic discharges ranges from 50 to 100 impulses per second.

[0375] Myotonia may be measured via electromyography and is graded in the following manner: grade 0 refers to no myotonia elicited by any needle insertion (0%); grade 1 refers to myotonia elicited by less than 50% needle insertions; grade 2 refers to myotonia elicited by more than 50% needle insertions; and grade 3 refers to mytonia elicited by 100% needle insertions.

[0376] Before electromyography, mice were anesthetized by using i.p. 100 mg/kg ketamine, 10 mg/kg xylazine, and 3 mg/kg acepromazine or 250 mg/kg 2,2,2-tribromoethanol. Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 24 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with ISIS 445236 and ISIS 445238.

TABLE 24

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	PBS	ISIS 190403	ISIS 445236	ISIS 445238
Left quadriceps	3.00	3.00	0.00	0.25
Right quadriceps	3.00	3.00	0.00	0.00
Left gastrocnemius	3.00	3.00	0.00	0.25
Right gastrocnemius	3.00	3.00	0.00	0.25
Left Tibialis anterior	2.75	2.50	0.00	0.00
Right Tibialis anterior	2.75	2.50	0.00	0.00
Lumbar paraspinals	3.00	3.00	0.00	0.75

Correction of Alternative Splicing

[0377] The splicing factor MBNL1, which controls Serca1 splicing, m-Titin splicing, CIC-1 chloride channel gene (Clcn1) splicing, and Zasp splicing, is sequestered in expanded CUG foci. MBNL1 sequestration triggers dysregulated splicing in each of these genes. To evaluate the effect of antisense inhibition of human alpha 1 actin on splicing, total RNA was purified from the tibialis anterior, gastrocnemius, and quadriceps muscle and RT-PCR was performed, as described in Example 13. The forward and reverse primers for Serca-1, m-Titin, Clcn1, and ZASP have been described in Bennett and Swayze, Annu. Rev. Pharmacol. 2010; 50: 259-93.

[0378] In PBS treated HSA^{LR} mice, Serca1 splicing is dysregulated as demonstrated by exon 22 exclusion. Treatment with each of ISIS 445236 and ISIS 445238 resulted in exon 22 inclusion and normalization of alternative splicing of the Serca1 gene in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0379] In PBS treated HSA^{LR} mice, m-Titin splicing is dysregulated as demonstrated by exon 5 inclusion. Treatment with each of ISIS 445236 and ISIS 445238 resulted in skipping of exon 5 and normalization of alternative splicing of the m-Titin gene in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0380] In PBS treated HSA^{LR} mice, Clcn1 splicing is dysregulated as demonstrated by exon 7a inclusion. Treatment with each of ISIS 445236 and ISIS 445238 resulted in skipping of exon 7a and normalization of alternative splicing of the Clcn1 gene in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0381] In PBS treated HSA^{LR} mice, Zasp splicing is dysregulated as demonstrated by exon 11 inclusion. Treatment with each of ISIS 445236 and ISIS 445238 resulted in skipping of exon 11 and normalization of alternative splicing of the Zasp gene in the tibialis anterior, gastrocnemius, and quadriceps muscles.

[0382] Therefore, antisense inhibition of alpha1 actin corrected Serca1, m-Titin, Clcn1, and Zasp splicing dysregulation, which indicates that treatment with antisense oligonucleotide reduced accumulation of CUGexp in the nuclear foci. Reduced accumulation of CUGexp in the nuclear foci correct MBLN1 sequestration thereby allowing normal splicing to occur.

Example 15

In Vivo Antisense Inhibition of Human Alpha1 Actin in Transgenic Mice

[0383] Antisense inhibition of human alpha1 actin RNA transcript by ISIS 445236 and ISIS 445238 on myotonia in HSA^{LR} mice was further evaluated.

Treatment

[0384] HSA^{LR} mice were divided into three treatment groups. The first two groups received subcutaneous injections of ISIS 445236 or ISIS 445238 at a dose of 25 mg/kg twice per week for 2 weeks. The third group received subcutaneous injections of PBS twice per week for 2 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Inhibition of Alpha1 Actin RNA

[0385] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles, gastrocnemius muscles, and tibialis anterior muscles was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 25, treatment with antisense oligonucleotides reduced human alpha1 actin RNA transcript expression. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

[0386] Both ISIS 445236 and ISIS 445238 demonstrated significant inhibition of alpha1 actin mRNA levels under the conditions specified above.

TABLE 25

Percent inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

Muscle Type	ISIS 445236	ISIS 445238
Quadriceps	61	64
Gastrocnemius	68	37
Tibialis anterior	68	41

Assessment of Myotonia by Electromyography

[0387] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 26 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with ISIS 445236 and ISIS 445238.

TABLE 26

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	PBS	ISIS 445236	ISIS 445238
Left quadriceps	3.00	0.00	1.75
Right quadriceps	3.00	0.00	1.75
Left gastrocnemius	3.00	0.25	1.5
Right gastrocnemius	3.00	0.25	1.00
Left Tibialis anterior	2.75	0.00	0.00
Right Tibialis anterior	2.75	0.00	0.00
Lumbar paraspinals	3.00	0.50	2.00

Correction of Alternative Splicing

[0388] To evaluate the effect of ISIS 190401 on alternative splicing of Serca1, total RNA purified from the tibialis anterior gastrocnemius, and quadriceps muscle was analyzed in a procedure similar to that described in Example 13.

[0389] In PBS treated HSA^{LR} mice, Serca1 splicing is dysregulated as demonstrated by exon 22 exclusion, as a result of MBLN1 dysregulation. Treatment with each of ISIS 445236 and ISIS 445238 resulted in near-complete inclusion and normalization of alternative splicing of exon 22 of the Serca1 gene in the tibialis anterior and quadriceps muscles.

[0390] Therefore, antisense inhibition of alpha1 actin corrected Serca1 splicing dysregulation, which indicates that treatment with antisense oligonucleotide reduced accumulation of CUGexp in the nuclear foci. Reduced accumulation of CUGexp in the nuclear foci correct MBLN1 sequestration thereby allowing normal splicing to occur.

Example 16

Dose-Dependent Antisense Inhibition of Human Alpha1 Actin in Transgenic Mice

[0391] Dose-dependent inhibition of human alpha1 actin RNA transcript by ISIS 445236 and ISIS 445238 on myotonia in HSA^{LR} mice was evaluated.

Treatment

[0392] HSA^{LR} mice were subcutaneously injected with ISIS 445236 or ISIS 445238 at doses of 2.5 mg/kg, 8.5 mg/kg or 25.0 mg/kg twice per week for 4 weeks. The control group received subcutaneous injections of PBS twice per week for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Inhibition of Alpha1 Actin RNA

[0393] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles (Quad), gastrocnemius muscles (Gastroc), and tibialis anterior muscles (TA) was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 27, treatment with antisense oligonucleotides reduced human alpha1 actin RNA transcript expression. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

[0394] Both the antisense oligonucleotides demonstrated dose-dependent inhibition of alpha1 actin mRNA levels in quadriceps muscles, gastrocnemius muscles, and tibialis anterior muscles under the conditions specified above.

TABLE 27

Dose-dependent inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

	mg/kg/wk	Quad	Gastroc	TA
ISIS 445236	5	24	36	46
	17	53	57	59
	50	86	86	90
ISIS 445238	5	21	37	3
	17	30	39	60
	50	59	81	70

Assessment of Myotonia by Electromyography

[0395] Electromyography on left and right quadriceps (Quad), left and right gastrocnemius muscles (Gastroc), left and right tibialis anterior (TA) muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 28 as the average myotonia grade observed in four mice of each group and demonstrates significant dose-dependent reduction of myotonia in mice treated with ISIS 445236 and ISIS 445238.

TABLE 28

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	mg/kg/wk	Left Quad	Right Quad	Left Gastroc	Right Gastroc	Left TA	Right TA	Lumbar paraspinals
PBS	—	3.00	3.00	3.00	3.00	2.75	2.75	3.00
ISIS 445236	5	3.00	3.00	3.00	3.00	2.25	2.25	3.00
	17	0.75	0.75	0.75	1.00	0.00	0.00	1.75
	50	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ISIS 445238	5	2.75	2.75	2.50	2.50	2.00	1.75	2.75
	17	3.00	3.00	2.00	2.25	0.00	0.00	2.75
	50	0.75	0.75	0.25	0.25	0.00	0.00	1.00

Correction of Alternative Splicing

[0396] To evaluate the effect of ISIS 190401 on alternative splicing of Serca1, total RNA purified from the tibialis anterior gastrocnemius, and quadriceps muscle was analyzed in a procedure similar to that described in Example 13.

[0397] In PBS treated HSA^{LR} mice, Serca1 splicing is dysregulated as demonstrated by exon 22 exclusion, as a result of MBLN1 dysregulation. Treatment with either ISIS 445236 or ISIS 445238 at doses of 8.5 mg/kg or 25.0 mg/kg twice a week (or 17.0 mg/kg/week and 50.0 mg/kg/week) resulted in complete inclusion and normalization of alternative splicing of exon 22 of the Serca1 gene in all three muscle types.

[0398] Therefore, antisense inhibition of alpha1 actin corrected Serca1 splicing dysregulation, which indicates that treatment with antisense oligonucleotide reduced accumulation of CUGexp in the nuclear foci. Reduced accumulation of CUGexp in the nuclear foci correct MBLN1 sequestration thereby allowing normal splicing to occur.

Example 17

In Vivo Antisense Inhibition by an Oligonucleotide Targeting the HSA Coding Region of Human Alpha1 Actin in Transgenic Mice

[0399] Antisense inhibition of human alpha1 actin RNA transcript by ISIS 190401 (5'-GCGGTCAGCGATCCCAGGGT-3' (SEQ ID NO: 788), target start site 1028 of SEQ ID NO: 1) on myotonia in HSA^{LR} mice was evaluated.

Treatment

[0400] HSA^{LR} mice received subcutaneous injections of ISIS 190401 at a dose of 25 mg/kg twice per week for 4 weeks. A control group received subcutaneous injections of PBS twice per week for 2 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Inhibition of Alpha1 Actin RNA

[0401] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles, gastrocnemius muscles, and tibialis anterior muscles was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 29, treatment with antisense oligonucleotides reduced human alpha1 actin RNA transcript expression. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

[0402] Treatment with ISIS 190401 resulted in significant inhibition of alpha1 actin mRNA levels in quadriceps muscle, gastrocnemius muscle, and tibialis anterior muscle under the conditions specified above.

TABLE 29

Antisense inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

Muscle Type	% inhibition
Quadriceps	85
Gastrocnemius	86
Tibialis anterior	89

Assessment of Myotonia by Electromyography

[0403] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 30 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with ISIS 190401.

TABLE 30

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	PBS	ISIS 190401
Left quadriceps	3.00	0.00
Right quadriceps	3.00	0.00
Left gastrocnemius	3.00	0.00
Right gastrocnemius	3.00	0.00
Left Tibialis anterior	2.50	0.00
Right Tibialis anterior	2.50	0.00
Lumbar paraspinals	3.00	0.50

Correction of Alternative Splicing

[0404] To evaluate the effect of ISIS 190401 on alternative splicing of Serca1, total RNA purified from the tibialis anterior gastrocnemius, and quadriceps muscle was analyzed in a procedure similar to that described in Example 13.

[0405] In PBS treated HSA^{LR} mice, Serca1 splicing is dysregulated as demonstrated by exon 22 exclusion, as a result of MBLN1 dysregulation. Treatment with ISIS 190401 resulted in complete inclusion and normalization of alternative splicing of exon 22 of the Serca1 gene in all three muscle types.

[0406] Therefore, antisense inhibition of alpha1 actin corrected Serca1 splicing dysregulation, which indicates that treatment with antisense oligonucleotide reduced accumulation of CUGexp in the nuclear foci. Reduced accumulation of

CUGexp in the nuclear foci corrects MBLN1 sequestration thereby allowing normal splicing to occur.

Example 18

Duration of Action of Antisense Inhibition by an Oligonucleotide Targeting Human Alpha1 Actin in Transgenic Mice

[0407] The duration of action of antisense inhibition of human alpha1 actin RNA transcript by ISIS 445236 in HSA^{LR} mice was evaluated.

Treatment

[0408] HSA^{LR} mice received subcutaneous injections of ISIS 445236 at a dose of 25 mg/kg twice per week for 4 weeks. A control group received subcutaneous injections of PBS twice per week for 2 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared. The mice were analyzed 6 weeks after administration of the last dose.

Inhibition of Alpha1 Actin RNA

[0409] Six weeks after the final dose, the animals were sacrificed and tissue from the quadriceps muscles, gastrocnemius muscles, and tibialis anterior muscles was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 31, treatment with ISIS 445236 reduced human alpha1 actin RNA transcript expression, and this effect was sustained at least for 6 weeks. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

[0410] Treatment with ISIS 445236 resulted in significant inhibition of alpha1 actin mRNA levels in quadriceps muscle, gastrocnemius muscle, and tibialis anterior muscle under the conditions specified above.

TABLE 31

Antisense inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

Muscle Type	% inhibition
Quadriceps	88
Gastrocnemius	76
Tibialis anterior	67

Assessment of Myotonia by Electromyography

[0411] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 32 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with ISIS 445236. Therefore, the effect of antisense inhibition of alpha actin by ISIS 445236 was sustained at least for 6 weeks.

TABLE 32

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	PBS	ISIS 445236
Left quadriceps	3.00	0.00
Right quadriceps	3.00	0.00
Left gastrocnemius	3.00	0.00
Right gastrocnemius	3.00	0.00
Left Tibialis anterior	2.50	0.00
Right Tibialis anterior	2.50	0.00
Lumbar paraspinals	3.00	0.00

Example 19

In Vivo Effect of Antisense Inhibition of mRNA with CUG Repeats by Intramuscular Administration in Transgenic Mice

[0412] The effect of antisense inhibition of mRNA transcripts containing multiple CUG repeats on myotonia in HSA^{LR} mice was evaluated. Three antisense oligonucleotides targeting the CUG repeats and with varying lengths were assayed for their effectiveness in inhibiting myotonia in the mice. ISIS 444745 (AGCAGCAGCAGCAGCAGCAG-CAGCA (SEQ ID NO: 789) is a uniform 2'-O-methoxyethyl oligonucleotide, 25 nucleotides in length and with a phosphorothioate backbone. ISIS 444746 (AGCAGCAGCAGCAG-CAGCAG (SEQ ID NO: 790) is a uniform 2'-O-methoxyethyl oligonucleotide, 20 nucleotides in length and with a phosphorothioate backbone. ISIS 444749 (GCAGCAG-CAGCAGCA (SEQ ID NO: 791) is a uniform 2'-O-methoxyethyl oligonucleotide, 15 nucleotides in length and with a phosphorothioate backbone. ISIS 445236 was included in the assay as a positive control.

Treatment

[0413] HSA^{LR} mice were divided into three treatment groups. The groups received direct intramuscular injections of ISIS 444745, ISIS 444746 or ISIS 444749 at a dose of 0.4 nM into the tibialis anterior muscle. The contralateral tibialis anterior muscle in each mouse received a single dose intramuscular injection of PBS. The PBS-injected muscle acted as the control.

Inhibition of Alpha1 Actin RNA

[0414] Twenty four hours after the final dose, the animals were sacrificed and tissue from the tibialis anterior (left and right) was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 33, only treatment with ISIS 444745 reduced human alpha1 actin RNA transcript expression. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

TABLE 33

Percent inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

ISIS No.	% inhibition
444745	51
444746	0
444749	12

Example 20

In Vivo Dose Dependent Inhibition of mRNA with CUG Repeats by Intramuscular Administration in Transgenic Mice

[0415] ISIS 444745 and ISIS 444746 were further evaluated for their ability to reduce human alpha 1 actin mRNA in vivo.

Treatment

[0416] HSA^{LR} mice were maintained on a 12-hour light/dark cycle and fed ad libitum normal Purina mouse chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. Antisense oligonucleotides (ASOs) were prepared in PBS and sterilized by filtering through a 0.2 micron filter. Oligonucleotides were dissolved in 0.9% PBS for injection.

[0417] The mice were divided into 6 treatment groups. Three of the groups received direct intramuscular injections of ISIS 444745 at doses of 0.2 nM, 0.5 nM, or 1.0 nM into the tibialis anterior muscle on one side. Another three groups direct intramuscular injections of ISIS 444746 at doses of 0.2 nM, 0.5 nM, or 1.0 nM into the tibialis anterior muscle on one side. The contralateral tibialis anterior muscle in each mouse received a single dose intramuscular injection of PBS. The PBS-injected muscle acted as the control for the corresponding muscle treated with ISIS oligonucleotide.

Assessment of Myotonia by Electromyography

[0418] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 34 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with either ISIS 444745 or ISIS 444746. The effect of antisense inhibition of alpha actin by ISIS 444745 and 444746 was sustained at least for 6 weeks.

TABLE 34

Dose-dependent reduction of myotonia in muscles of antisense oligonucleotide-treated HSA^{LR} mice

	0.2 nM	0.5 nM	1.0 nM
PBS	3.00	3.00	2.33
ISIS 444745	1.67	1.00	0.33
PBS	2.50	2.00	3.00
ISIS444746	2.00	0.00	1.00

Example 21

In Vivo Effect of Antisense Inhibition of mRNA with CUG Repeats by Subcutaneous Administration in Transgenic Mice

[0419] The effect of antisense inhibition of mRNA transcripts containing multiple CUG repeats on myotonia in HSA^{LR} mice was evaluated. ISIS 445236 was included in the assay as a positive control.

Treatment

[0420] HSA^{LR} mice were divided into five treatment groups. The first three groups received subcutaneous injections of ISIS 444745, ISIS 444746 or ISIS 444749 at a dose of 25 mg/kg twice per week for 4 weeks. The fourth group received subcutaneous injections of PBS twice per week for 4 weeks. The fifth group received subcutaneous injections of ISIS 445236 at a dose of 25 mg/kg twice per week for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Assessment of Myotonia by Electromyography

[0421] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 35 as the average myotonia grade observed in four mice of each group.

[0422] Treatment with ISIS 445236 led to significant reduction in myotonia. Treatment with ISIS 444745 and ISIS 444746 also resulted in reduced myotonia in some of the tissues tested.

TABLE 35

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	PBS	ISIS 444745	ISIS 444746	ISIS 444749	ISIS 445236
Left quadriceps	3.00	3.00	3.00	3.00	0.00
Right quadriceps	3.00	3.00	3.00	3.00	0.00
Left gastrocnemius	3.00	2.75	3.00	3.00	0.00
Right gastrocnemius	3.00	2.75	2.75	3.00	0.00
Left Tibialis anterior	3.00	2.25	2.75	2.75	0.00
Right Tibialis anterior	3.00	2.25	2.50	2.75	0.00
Lumbar paraspinals	3.00	3.00	3.00	3.00	0.00

Example 22

Dose-Dependent Inhibition of Long CUG Repeat mRNA (HSA^{LR} Mice) and a Short CUG Repeat (HSA^{SR} Mice) by Subcutaneous Administration in Transgenic Mice

[0423] Dose-dependent inhibition of mRNA transcripts containing a long CUG repeat (HSA^{LR} mice) and a short CUG repeat (HSA^{SR} mice), was evaluated. HSA-short repeat (HSA^{SR}) mice express the identical transgene as the HSA^{LR} mice, except that 5 instead of 250 CUG repeats are inserted in the 3' UTR. HSA^{SR} mice do not have myotonia, splicing

changes, or any other observable myotonia phenotype. ISIS 445236 was used in this assay.

Treatment

[0424] HSA^{LR} mice were divided into four treatment groups. The first three groups received subcutaneous injections of ISIS 445236 at doses of 2.5 mg/kg, 8.5 mg/kg or 25.0 mg/kg twice per week for 4 weeks. The fourth group received subcutaneous injections of PBS twice per week for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared. HSA^{SR} mice were also divided into four groups and similarly treated.

Inhibition of Alpha1 Actin RNA

[0425] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles (left and right), gastrocnemius muscles (left and right), and tibialis anterior muscles (left and right) was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. The results are presented in Tables 36 and 37 and are expressed as percent inhibition of alpha1 actin transcript, relative to the control. Greater inhibition of the nuclear-retained long repeat in the muscle of HSA^{LR} mice was achieved compared with the non-nuclear-retained short repeat in the muscle of HSA^{SR} mice.

TABLE 36

Percent inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

Dose (mg/kg)	Quadriceps	Gastrocnemius	Tibialis anterior
2.5	24	36	46
8.5	53	66	59
25	86	86	90

TABLE 37

Percent inhibition of human alpha1 actin RNA transcript in HSA^{SR} mice

Dose (mg/kg)	Quadriceps	Gastrocnemius	Tibialis anterior
2.5	15	14	0
8.5	30	11	0
25	59	48	54

Example 23

In Vivo Antisense Inhibition of Human DMPK in Transgenic Mice

[0426] LC15 mice, Line A, are transgenic mice containing the entire human DMPK 3'UTR (developed by Wheeler et al, University of Rochester). The mice are the second generation of mice backcrossed to an FVB background. The transgene is expressed in the mice as a CUG repeat RNA, which is retained in the nucleus, forming nuclear inclusions or foci, similar to that seen in human tissue samples of patients with myotonic dystrophy (DM1). There are 350-400 CUG repeats in the DMPK transgene. These mice display early signs of DM1 and do not display any myotonia in their muscle tissues.

[0427] ISIS 445569, ISIS 444404, ISIS 444436 and ISIS 473810, which demonstrated statistically significant dose-dependent inhibition in vitro (see Example 5), were evaluated for their ability to reduce human DMPK RNA transcript in vivo.

Treatment

[0428] LC15, Line A mice were maintained on a 12-hour light/dark cycle and fed ad libitum normal Purina mouse chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. Antisense oligonucleotides (ASOs) were prepared in PBS and sterilized by filtering through a 0.2 micron filter. Oligonucleotides were dissolved in 0.9% PBS for injection.

[0429] The mice were divided into five treatment groups. The first three groups received subcutaneous injections of ISIS 445569, ISIS 444404 or ISIS 444436 at a dose of 25 mg/kg twice per week for 4 weeks. The fourth group received subcutaneous injections of ISIS 473810 at a dose of 12.5 mg/kg twice per week for 4 weeks. The fifth group received subcutaneous injections of PBS twice weekly for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Inhibition of DMPK RNA

[0430] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles was isolated. RNA was isolated for real-time PCR analysis of DMPK and normalized to 18s RNA. As presented in Table 38, treatment with antisense oligonucleotides reduced human DMPK RNA transcript expression. The results are expressed as percent inhibition of DMPK transcript, relative to the PBS control.

TABLE 38

Antisense inhibition of human DMPK RNA transcript in LC15 mice

ISIS No	mg/kg/wk	% inhibition
444404	50	20
444404	50	55
444436	50	41
473810	25	56

Assessment of Myotonia by Electromyography

[0431] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. Since LC15 mice do not have myotonia, neither the control group nor the treatment groups displayed any myotonia in any muscle tested.

Example 24

In Vivo Antisense Inhibition of Human DMPK in Transgenic Mice

[0432] LC15 mice, Line D, are transgenic mice containing the entire human DMPK 3'UTR (developed by Wheeler et al,

University of Rochester). The mice are the third generation of mice backcrossed to an FVB background. The transgene is expressed in the mice as a CUG repeat RNA, which is retained in the nucleus, forming nuclear inclusions or foci, similar to that seen in human tissue samples of patients with myotonic dystrophy (DM1). There are 350-400 CUG repeats in the DMPK transgene. These mice display early signs of DM1 and do not display any myotonia in their muscle tissues.

[0433] ISIS 445569, ISIS 444404, ISIS 444436 and ISIS 473810 were further evaluated for their ability to reduce human DMPK RNA transcript in vivo.

Treatment

[0434] LC15, Line D mice were maintained on a 12-hour light/dark cycle and fed ad libitum normal Purina mouse chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. Antisense oligonucleotides (ASOs) were prepared in PBS and sterilized by filtering through a 0.2 micron filter. Oligonucleotides were dissolved in 0.9% PBS for injection.

[0435] The mice were divided into six treatment groups. The first three groups received subcutaneous injections of ISIS 445569, ISIS 444404 or ISIS 444436 at a dose of 25.00 mg/kg twice per week for 4 weeks. The fourth group received subcutaneous injections of ISIS 473810 at a dose of 12.50 mg/kg twice per week for 4 weeks. The fifth group received subcutaneous injections of ISIS 473810 at a dose of 6.25 mg/kg twice per week for 4 weeks. The sixth group received subcutaneous injections of PBS twice weekly for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Inhibition of DMPK RNA

[0436] Twenty four hours after the final dose, the animals were sacrificed and tissue from the quadriceps muscles was isolated. RNA was isolated for real-time PCR analysis of DMPK and normalized to 18s RNA. As presented in Table 39, treatment with antisense oligonucleotides reduced human DMPK RNA transcript expression. The results are expressed as percent inhibition of DMPK transcript, relative to the PBS control.

[0437] The results indicate that treatment with the antisense oligonucleotides resulted in inhibition of DMPK mRNA in the mice.

TABLE 39

Antisense inhibition of human DMPK RNA transcript in LC15 mice

ISIS No	mg/kg/wk	% inhibition
444404	50.00	24
444404	50.00	30
444436	50.00	17
473810	25.00	7
473810	12.50	18

Assessment of Myotonia by Electromyography

[0438] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. Since LC15 mice do not have myotonia, neither the control group nor the treatment groups displayed any myotonia in any muscle tested.

Example 25

In Vivo Antisense Inhibition of Human DMPK in SXL Transgenic Mouse Model

[0439] Using hDMPK-targeting ASOs 444401 and 299471 target knockdown in soleus muscle was measured in SXL mice. The SXL mouse is transgenic for the entire DMPK gene and promoter and contains a 1000 CUG repeat sequence in the 3'UTR of DMPK gene. Mice were dosed 50 mg/kg twice weekly for 4 weeks (n=3 mice per group, except n=2 for saline-injected controls). Results of Taqman assays demonstrated that treatment with either ISISI 444401 or ISIS 299471 significantly reduced mut-hDMPK mRNA levels but had negligible effect on endogenous mouse Dmpk mRNA levels.

[0440] Therefore, ISIS 444401 and ISIS 299471 selectively target human DMPK mRNA transcript.

Example 26

Duration of Action of Antisense Inhibition by an Oligonucleotide Targeting Human Alpha1 Actin in Transgenic Mice

[0441] The duration of action of antisense inhibition of human alpha1 actin RNA transcript by ISIS 190401 in HSA^{LR} mice was evaluated.

Treatment

[0442] HSA^{LR} mice received subcutaneous injections of ISIS 190401 at a dose of 25 mg/kg twice per week for 4 weeks. A control group received subcutaneous injections of PBS twice per week for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared. The mice were analyzed 15 weeks after administration of the last dose.

Inhibition of Alpha1 Actin RNA

[0443] Fifteen weeks after the final dose, the animals were sacrificed and tissue from the quadriceps muscles, gastrocnemius muscles, and tibialis anterior muscles was isolated. RNA was isolated for real-time PCR analysis of alpha1 actin and normalized to 18s RNA. As presented in Table 40, treatment with ISIS 190401 reduced human alpha1 actin RNA transcript expression, and this effect was sustained at least for 15 weeks. The results are expressed as percent inhibition of alpha1 actin transcript, relative to the PBS control.

[0444] Treatment with ISIS 190401 resulted in significant inhibition of alpha1 actin mRNA levels under the conditions specified above.

TABLE 40

Antisense inhibition of human alpha1 actin RNA transcript in HSA^{LR} mice

Muscle Type	% inhibition
Quadriceps	74
Gastrocnemius	81
Tibialis anterior	75

Assessment of Myotonia by Electromyography

[0445] Electromyography on left and right quadriceps, left and right gastrocnemius muscles, left and right tibialis anterior muscles and lumbar paraspinals muscles was performed as previously described (Kanadia et al, 2003, Science, 302: 1978-1980) by using 30 gauge concentric needle electrodes and a minimum of 10 needle insertions for each muscle. The data is presented in Table 41 as the average myotonia grade observed in four mice of each group and demonstrates significant reduction of myotonia in mice treated with ISIS 190401. Therefore, the effect of antisense inhibition of alpha actin by ISIS 190401 was sustained at least for 15 weeks.

TABLE 41

Average reduction of myotonia in various muscles of antisense oligonucleotide-treated HSA^{LR} mice

	PBS	ISIS 190401
Left quadriceps	3.0	0.0
Right quadriceps	3.0	0.0
Left gastrocnemius	2.5	0.0
Right gastrocnemius	2.5	0.0
Left Tibialis anterior	2.5	0.0
Right Tibialis anterior	2.5	0.0
Lumbar paraspinals	2.5	0.0

Correction of Alternative Splicing

[0446] To evaluate the effect of ISIS 190401 on alternative splicing of Serca1, total RNA purified from the tibialis anterior gastrocnemius, and quadriceps muscle was analyzed in a procedure similar to that described in Example 13.

[0447] In PBS treated HSA^{LR} mice, Serca1 splicing is dysregulated as demonstrated by exon 22 exclusion. Treatment with ISIS 190401 resulted in complete inclusion and normalization of alternative splicing of exon 22 of the Serca1 gene in all three muscle types, which was sustained even after 15 weeks.

[0448] Therefore, antisense inhibition of alpha1 actin corrected Serca1 splicing dysregulation, which indicates that treatment with antisense oligonucleotide reduced accumulation of CUGexp in the nuclear foci. Reduced accumulation of CUGexp in the nuclear foci corrects MBLN1 sequestration thereby allowing normal splicing to occur.

Example 27

Microarray Analysis of Transcriptomic Effect of Antisense Inhibition of Human Actin

[0449] Expression of actin mRNA with expanded CUG repeats causes extensive remodeling of the muscle transcriptome. To evaluate the overall transcriptomic effects of ISIS 190401 and ISIS 445236, microarray analyses was utilized in HSA^{LR} mice.

Treatment

[0450] HSA^{LR} mice received subcutaneous injections of ISIS 190401 or ISIS 445236 at a dose of 25 mg/kg twice per week for 4 weeks. A control group received subcutaneous injections of PBS twice per week for 4 weeks. The PBS-injected group served as the control group to which the oligonucleotide-treated group was compared.

Transcriptome Analysis by Microarray

[0451] RNA was isolated from the quadriceps muscle of wild-type or HSA^{LR} mice. RNA integrity was verified using an Agilent Bioanalyzer (RNA integrity number >7.5). RNA was processed to complementary RNA (cRNA) and hybridized on microbeads using MouseRef-8 v2.0 Expression BeadChip Kits (Illumina, San Diego), according to the manufacturer's recommendations. Image data were quantified using BeadStudio software (Illumina). Signal intensities were quantile normalized. Row-specific offsets were used to avoid any values of less than 2 prior to normalization. Data from all probe sets with 6 or more nucleotides of CUG, UGC, or GCU repeats was suppressed to eliminate the possibility that expanded repeats in the hybridization mixture (CAG repeats in cRNA originating from CUG repeats in the mRNA) could cross-hybridize with repeat sequences in the probes. To eliminate genes whose expression was not readily quantified on the arrays, probes showing a P value for detection probability of <0.1 were suppressed in all samples. Comparisons between groups were summarized and rank-ordered by fold-changes of mean expression level and t tests. The software package R (Butler et al. *Diabetes.* 2002; 51: 1028-34) was used to perform principal components analysis (Levin et al. In *Antisense Drug Technology: Principles, Strategies, and Applications*, S.T. Crooke, Ed. (CRC Press, Boca Raton, 2008), pp 183-215; Geary et al. *Drug Metab. Dispos.* 2003; 31: 1419-28) on wild-type, ISIS oligonucleotide-treated, and PBS-treated microarray samples. The principle components allowed the capture of the majority of the expression variation in each sample within 3 dimensions. The first three principal components of each sample were plotted.

[0452] The principle component analysis of untreated wild-type and HSA^{LR} mice demonstrated segregation of HSA^{LR} away from wild-type mice, in widely separated clusters. In contrast, antisense oligonucleotide-treated HSA^{LR} mice clustered more closely to wild-type mice, suggesting an overall trend for transcriptome normalization. Comparisons of HSA^{LR} transgenic mice with wild-type mice identified 93 transcripts whose expression levels were altered more than two-fold (P<0.0001), as presented in Table 42, below. The extent of dysregulation for these transcripts was reduced or normalized for antisense oligonucleotides (88% dysregulated transcripts responded to ISIS 445236, P<0.05 for ISIS 445236 vs. PBS control, whereas 90% responded to ISIS 190401).

[0453] In order to consider transcripts that have off-target knockdown, all transcripts whose expression was reduced in antisense oligonucleotide-treated HSA^{LR} mice were identified (>two-fold reduction by either oligonucleotide, P<0.0001, n=41 transcripts). All transcripts that were down-regulated by these criteria demonstrated upregulation in HSA^{LR}

mice. The only exception, collagen 6 alpha2, is unlikely to result from off-target cleavage because it was down-regulated by the two antisense oligonucleotides with non-overlapping sequences.

[0454] These results indicate that treatment with antisense oligonucleotides for 4 weeks resulted in a general improvement of the muscle transcriptome without any evidence for off-target effects.

TABLE 42

Comparisons of HSA^{LR} transgenic mice with wild-type mice identified 93 transcripts

Transcript	Fold-change HSALR-saline vs. WT	t test HSALR - Saline vs. WT	Fold-change HSALR-190104 vs. HSALR-saline	t test HASLR 190401 vs. HSALR - saline	Fold-change HSALR-190401 vs. WT	t test HSALR-190401 vs. WT	Fold-change HSALR-445236 vs. HSALR-saline	t test HSALR-445236 vs. HSALR-saline	Fold-change HSALR-445236 vs. WT	t test HSALR-445236 vs. WT
OSBPL10	15.11	0.0000	0.46	0.0023	6.95	0.0008	0.39	0.0007	5.92	0.0002
FBXL13	12.12	0.0000	0.49	0.0159	5.91	0.0385	0.65	0.0255	7.93	0.0026
NGFR	11.57	0.0000	0.23	0.0001	2.66	0.0314	0.16	0.0000	1.84	0.0133
SLC1A1	9.39	0.0000	0.39	0.0001	3.66	0.0001	0.30	0.0001	2.85	0.0116
CXADR	9.13	0.0000	0.14	0.0000	1.30	0.6119	0.21	0.0001	1.94	0.2244
NFATC2	8.48	0.0000	0.32	0.0002	2.67	0.0043	0.22	0.0001	1.84	0.0394
ATP1B4	7.02	0.0000	0.24	0.0000	1.68	0.0021	0.24	0.0000	1.70	0.0091
UCHL1	6.80	0.0000	0.71	0.0168	4.86	0.0005	0.72	0.1187	4.91	0.0090
TEAD4	6.76	0.0000	0.50	0.0030	3.39	0.0085	0.30	0.0004	2.06	0.1213
TAS1R1	6.72	0.0000	0.28	0.0003	1.91	0.1857	0.43	0.0002	2.88	0.0047
MUSTN1	6.52	0.0000	0.31	0.0000	2.01	0.0006	0.33	0.0000	2.15	0.0115
IRF5	6.01	0.0000	0.21	0.0000	1.28	0.0556	0.33	0.0001	1.96	0.0035
CRIP3	5.82	0.0000	0.33	0.0000	1.92	0.0151	0.29	0.0001	1.67	0.1470
TAL2	5.75	0.0000	0.20	0.0001	1.13	0.7717	0.36	0.0002	2.08	0.0274
ORF63	5.39	0.0000	0.27	0.0001	1.45	0.0206	0.47	0.0018	2.51	0.0066
COPG	5.05	0.0000	0.30	0.0000	1.53	0.0218	0.25	0.0001	1.25	0.3617
CAMK1D	4.92	0.0000	0.23	0.0002	1.12	0.8157	0.27	0.0000	1.32	0.2449
HSPA2	4.76	0.0000	0.43	0.0000	2.02	0.0079	0.42	0.0000	2.02	0.0197
CAMK2D	4.70	0.0000	0.36	0.0001	1.70	0.0493	0.45	0.0004	2.12	0.0095
CNTNAP2	4.49	0.0000	0.58	0.0001	2.59	0.0000	0.67	0.0007	3.02	0.0000
TTC7	4.33	0.0000	0.38	0.0000	1.63	0.0085	0.68	0.0468	2.96	0.0126
CD276	4.08	0.0001	0.36	0.0001	1.47	0.1613	0.59	0.0029	2.39	0.0072
USH1C	4.07	0.0000	0.50	0.0011	2.04	0.0077	0.38	0.0029	1.55	0.2881
LRP11	4.03	0.0000	0.55	0.0017	2.24	0.0011	0.55	0.0006	2.23	0.0000
PHLDA3	3.96	0.0000	0.40	0.0001	1.60	0.0019	0.36	0.0001	1.42	0.0609
HSPB7	3.80	0.0000	0.30	0.0000	1.14	0.5358	0.30	0.0000	1.15	0.4474
TRIT1	3.74	0.0000	0.43	0.0000	1.62	0.0003	0.31	0.0000	1.16	0.1043
PCNX	3.66	0.0000	0.37	0.0002	1.34	0.1628	0.42	0.0001	1.53	0.0105
3632451O06RIK	3.51	0.0000	0.81	0.1094	2.83	0.0025	0.71	0.0015	2.51	0.0002
AMHR2	3.46	0.0000	0.45	0.0001	1.56	0.0037	0.52	0.0003	1.79	0.0016
SNX13	3.27	0.0000	0.47	0.0000	1.55	0.0007	0.44	0.0000	1.42	0.0003
ATP9A	3.26	0.0000	0.60	0.0001	1.96	0.0024	0.42	0.0002	1.38	0.2009
D030028O16RIK	3.22	0.0000	0.53	0.0011	1.70	0.0104	0.48	0.0001	1.56	0.0007
RPS6KA3	3.09	0.0000	0.38	0.0000	1.17	0.1845	0.44	0.0001	1.37	0.0321
GCA	3.00	0.0000	0.70	0.0031	2.09	0.0005	0.74	0.0103	2.22	0.0006
PACRG	2.89	0.0001	0.51	0.0002	1.46	0.0063	0.46	0.0001	1.34	0.0229
SPSB2	2.88	0.0001	0.33	0.0000	0.95	0.6599	0.37	0.0000	1.07	0.6216
POU4F1	2.83	0.0000	0.42	0.0000	1.19	0.2046	0.60	0.0007	1.68	0.0074
STRN4	2.72	0.0000	0.38	0.0000	1.03	0.8900	0.46	0.0000	1.25	0.2128
NCAM1	2.67	0.0001	0.70	0.0259	1.87	0.0135	0.54	0.0006	1.43	0.0343
A930018M24Rik	2.65	0.0001	0.58	0.0058	1.53	0.0727	0.43	0.0002	1.13	0.3919
TUBA4A	2.60	0.0000	0.42	0.0000	1.09	0.1806	0.50	0.0000	1.31	0.0041
IAP	2.57	0.0000	0.57	0.0002	1.46	0.0108	0.59	0.0016	1.52	0.0333
ANKRD40	2.56	0.0000	0.63	0.0155	1.60	0.0683	0.57	0.0002	1.46	0.0047
UVRAG	2.48	0.0000	0.59	0.0000	1.48	0.0005	0.52	0.0000	1.28	0.0165
HIST1H4H	2.46	0.0001	0.55	0.0001	1.34	0.0474	0.65	0.0014	1.60	0.0125
EPS15	2.44	0.0000	0.61	0.0001	1.50	0.0057	0.77	0.0043	1.87	0.0007
PANX1	2.41	0.0001	0.46	0.0004	1.11	0.4311	0.36	0.0000	0.87	0.0561
CALML4	2.41	0.0001	0.45	0.0008	1.10	0.6994	0.67	0.0154	1.62	0.0538
ASPH	2.40	0.0000	0.40	0.0000	0.95	0.6969	0.44	0.0000	1.05	0.7267
CREB3L2	2.37	0.0001	0.71	0.0287	1.67	0.0416	0.65	0.0051	1.54	0.0410
TRAF3	2.32	0.0001	0.50	0.0001	1.16	0.2851	0.57	0.0001	1.32	0.0481
CMYA1	2.30	0.0000	0.44	0.0007	1.02	0.9450	0.44	0.0000	1.01	0.9265
ADAMTSL5	2.30	0.0001	0.48	0.0000	1.11	0.3365	0.53	0.0004	1.22	0.1827
HS2ST1	2.27	0.0001	0.64	0.0002	1.44	0.0223	0.74	0.0041	1.68	0.0062
HIST1H4J	2.21	0.0000	0.59	0.0000	1.31	0.0283	0.72	0.0002	1.60	0.0023
SPSB1	2.20	0.0000	0.53	0.0005	1.16	0.2409	0.48	0.0000	1.05	0.3088
LANCL1	2.20	0.0000	0.63	0.0002	1.39	0.0002	0.66	0.0006	1.46	0.0005
KCNC4	2.16	0.0000	0.91	0.3892	1.96	0.0036	0.98	0.8712	2.12	0.0029
PRRC1	2.16	0.0000	0.57	0.0001	1.23	0.0324	0.59	0.0000	1.26	0.0070
MID1IP1	2.13	0.0001	1.27	0.0161	2.70	0.0001	1.09	0.4336	2.32	0.0014
DICER1	2.13	0.0000	0.65	0.0006	1.39	0.0051	0.69	0.0018	1.47	0.0035

TABLE 42-continued

Comparisons of HSA^{LR} transgenic mice with wild-type mice identified 93 transcripts

Transcript	Fold-change HSALR-saline vs. WT	t test HSALR - Saline vs. WT	Fold-change HSALR-190104 vs. HSALR-saline	t test HASLR 190401 vs. HSALR - saline	Fold-change HSALR-190401 vs. WT	t test HSALR-190401 vs. WT	Fold-change HSALR-445236 vs. HSALR-saline	t test HSALR-445236 vs. HSALR-saline	Fold-change HSALR-445236 vs. WT	t test HSALR-445236 vs. WT
IKBKB	2.10	0.0001	0.74	0.0240	1.56	0.0262	0.78	0.0039	1.64	0.0015
D5WSU178E	2.10	0.0000	0.86	0.1447	1.80	0.0049	0.88	0.0352	1.84	0.0002
ZFP106	2.08	0.0000	0.53	0.0000	1.11	0.1324	0.58	0.0002	1.20	0.0706
B930041F14RIK	2.06	0.0000	0.71	0.0002	1.47	0.0000	0.72	0.0030	1.49	0.0025
FHL1	2.04	0.0000	0.58	0.0000	1.17	0.1332	0.40	0.0000	0.81	0.0815
UHRF1BP1L	2.04	0.0001	0.78	0.0315	1.59	0.0071	0.68	0.0024	1.38	0.0151
PHCA	2.02	0.0000	0.64	0.0001	1.29	0.0354	0.74	0.0070	1.50	0.0145
B230312A22RIK	2.02	0.0000	0.79	0.0022	1.59	0.0004	0.77	0.0019	1.56	0.0007
PPP2R5C	2.01	0.0000	0.59	0.0001	1.16	0.0161	0.66	0.0017	1.32	0.0177
UCK2	2.01	0.0001	0.70	0.0004	1.41	0.0129	0.64	0.0001	1.28	0.0510
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2688

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tcctgggact ggagcccctg ctcgaccttc tcctgggcgt ccaccaggag ctgggtgcct 240

ctcacctagc ccaggacaag tatgtggccg acttcttgca gtgggtggag cccattgcag 300

caaggcttaa ggaggtccga ctgcagaggg atgattttga gattttgaag gtgatcgggc 360

gtggggcgtt cagcgaggta gcggtggtga agatgaaaca gacgggccaa gtgtatgcca 420

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aaagggatgt attagtgaaa ggggaccggc gctggatcac acagctgcac tttgccttcc 540

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tgctgagcaa gtttggggag cggatccccg ccgagatggc tcgcttctac ctggccgaga 660

ttgtcatggc catagactcc gtgcaccggc tgggctacgt gcacagggac atcaaaccag 720

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tccgctcctg tgatccaggc ctgccacctg gcggccgggg agggaggaac agggctcgtg 2340

cccagcaccc ctggttcctg cagagctggt agccaccgct gctgcagcag ctgggcattc 2400

gccgaccttg ctttactcag ccccgacgtg gatgggcaaa ctgctcagct catccgattt 2460

cacttttca ctctcccagc catcagttac aagccataag catgagcccc ctatttccag 2520

ggacatccca ttcccatagt gatggatcag caagacctct gccagcacac acggagtctt 2580

tggcttcgga cagcctcact cctgggggtt gctgcaactc cttccccgtg tacacgtctg 2640

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ctcgacattc ctcggtattt attgtctgtc cccacctacg acctccactc ccgacccttg 2820

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<210> SEQ ID NO 10
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 10

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<210> SEQ ID NO 11
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 11

aggccatccg cacggacaac c 21

<210> SEQ ID NO 12
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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ctggctgcat gtctgcctgt 20

<210> SEQ ID NO 13
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 13

ccaggagaag gtcgagcagg 20

<210> SEQ ID NO 14
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<400> SEQUENCE: 14

tctatggcca tgacaatctc 20

<210> SEQ ID NO 15
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 15

atgtccctgt gcacgtagcc 20

<210> SEQ ID NO 16
<211> LENGTH: 20
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<400> SEQUENCE: 16

atgtgtccgg aagtcgcctg 20

<210> SEQ ID NO 17
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 17

ctcaggctct gccgggtgag 20

<210> SEQ ID NO 18
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 18

ggcactggcc cacagccacg 20

<210> SEQ ID NO 19
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cctggccgaa agaaagaaat 20

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aaagaaatgg tctgtgatcc 20

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aagaaagaaa tggtctgtga 20

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<400> SEQUENCE: 22

ggccgaaaga aagaaatggt 20

<210> SEQ ID NO 23
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cctcagcctg gccgaaagaa 20

<210> SEQ ID NO 24
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<212> TYPE: DNA
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<400> SEQUENCE: 24

gggcctcagc ctggccgaaa 20

<210> SEQ ID NO 25
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<212> TYPE: DNA
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<220> FEATURE:
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<210> SEQ ID NO 26

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<220> FEATURE:
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<400> SEQUENCE: 27

ggcctgcagt ttgcccatcc 20

<210> SEQ ID NO 28
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 28

ccaggcctgc agtttgccca 20

<210> SEQ ID NO 29
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<400> SEQUENCE: 29

gccttcccag gcctgcagtt 20

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

<400> SEQUENCE: 30

gctgccttcc caggcctgca 20

<210> SEQ ID NO 31
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 31

cttgctgcct tcccaggcct 20

<210> SEQ ID NO 32
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 32

gcccggcttg ctgccttccc 20

<210> SEQ ID NO 33
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 33

acggcccggc ttgctgcctt 20

<210> SEQ ID NO 34
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<212> TYPE: DNA
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cggacggccc ggcttgctgc 20

<210> SEQ ID NO 35
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 35

acacggacgg cccggcttgc 20

<210> SEQ ID NO 36
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<212> TYPE: DNA
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<400> SEQUENCE: 36

gatggaacac ggacggcccg 20

<210> SEQ ID NO 37
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 37

gaggatggaa cacggacggc 20

<210> SEQ ID NO 38
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 38

gtggaggatg gaacacggac 20

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<210> SEQ ID NO 39
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<212> TYPE: DNA
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<400> SEQUENCE: 39

gcgaaccaac gataggtggg 20

<210> SEQ ID NO 40
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 40

tttgcgaacc aacgataggt 20

<210> SEQ ID NO 41
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 41

ttgcactttg cgaaccaacg 20

<210> SEQ ID NO 42
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<212> TYPE: DNA
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<400> SEQUENCE: 42

gctttgcact ttgcgaacca 20

<210> SEQ ID NO 43
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 43

aaagctttgc actttgcgaa 20

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 44

aagaaagctt tgcactttgc 20

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 45

cacaagaaag ctttgcactt 20

<210> SEQ ID NO 46
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 46

gtcatgcaca agaaagcttt 20

<210> SEQ ID NO 47
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 47

acgctcccca gagcagggcg 20

<210> SEQ ID NO 48
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 48

gcagagatcg cgccagacgc 20

<210> SEQ ID NO 49
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 49

caggcagaga tcgcgccaga 20

<210> SEQ ID NO 50
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 50

aagcaggcag agatcgcgcc 20

<210> SEQ ID NO 51
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 51

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ccgagtaagc aggcagagat 20

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 52

ttcccgagta agcaggcaga 20

<210> SEQ ID NO 53
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 53

gcaaatttcc cgagtaagca 20

<210> SEQ ID NO 54
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 54

aaagcaaatt tcccgagtaa 20

<210> SEQ ID NO 55
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 55

ttggcaaaag caaatttccc 20

<210> SEQ ID NO 56
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 56

ggtttggcaa aagcaaattt 20

<210> SEQ ID NO 57
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 57

gcgggtttgg caaaagcaaa 20

<210> SEQ ID NO 58
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 58

aaagcgggtt tggcaaaagc 20

<210> SEQ ID NO 59
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 59

cccgaaaaag cgggtttggc 20

<210> SEQ ID NO 60
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 60

atccccgaaa aagcgggttt 20

<210> SEQ ID NO 61
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 61

cgggatcccc gaaaaagcgg 20

<210> SEQ ID NO 62
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 62

gcgcgggatc cccgaaaaag 20

<210> SEQ ID NO 63
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 63

gagagcagcg caagtgagga 20

<210> SEQ ID NO 64
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 64

tccgagagca gcgcaagtga 20

<210> SEQ ID NO 65
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 65

ggctccgaga gcagcgcaag 20

<210> SEQ ID NO 66
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 66

aagcgggcgg agccggctgg 20

<210> SEQ ID NO 67
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 67

ccgaagcggg cggagccggc 20

<210> SEQ ID NO 68
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 68

aaaccgccga agcgggcgga 20

<210> SEQ ID NO 69
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 69

tccaaaccgc cgaagcgggc 20

<210> SEQ ID NO 70
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 70

atatccaaac cgccgaagcg 20

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<210> SEQ ID NO 71
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 71

taaatatcca aaccgccgaa 20

<210> SEQ ID NO 72
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 72

caataaatat ccaaaccgcc 20

<210> SEQ ID NO 73
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 73

cgaggtcaat aaatatccaa 20

<210> SEQ ID NO 74
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 74

ggacgaggtc aataaatatc 20

<210> SEQ ID NO 75
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 75

ggaggacgag gtcaataaat 20

<210> SEQ ID NO 76
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 76

gtcggaggac gaggtcaata 20

<210> SEQ ID NO 77
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 77

cgagtcggag gacgaggtca 20

<210> SEQ ID NO 78
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 78

tgtcagcgag tcggaggacg 20

<210> SEQ ID NO 79
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 79

gcctgtcagc gagtcggagg 20

<210> SEQ ID NO 80
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 80

gtagcctgtc agcgagtcgg 20

<210> SEQ ID NO 81
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 81

cctgtagcct gtcagcgagt 20

<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 82

ggtcctgtag cctgtcagcg 20

<210> SEQ ID NO 83
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 83

aaataccgag gaatgtcggg 20

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<210> SEQ ID NO 84
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 84

aataaatacc gaggaatgtc 20

<210> SEQ ID NO 85
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 85

gacaataaat accgaggaat 20

<210> SEQ ID NO 86
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 86

cggggccccg gagtcgaaga 20

<210> SEQ ID NO 87
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 87

ccaacggggc cccggagtcg 20

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 88

ttccaacggg gccccggagt 20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 89

gtcttccaac ggggccccgg 20

<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 90

cagtcttcca acggggcccc 20

<210> SEQ ID NO 91
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 91

ctcagtcttc caacggggcc 20

<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 92

gcactcagtc ttccaacggg 20

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

<400> SEQUENCE: 93

ccccgggcac tcagtcttcc 20

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

<400> SEQUENCE: 94

tgccccgggc actcagtctt 20

<210> SEQ ID NO 95
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 95

cgtgccccgg gcactcagtc 20

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

<400> SEQUENCE: 96

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gtgccgtgcc ccgggcactc 20

<210> SEQ ID NO 97
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 97

tctgtgccgt gccccgggca 20

<210> SEQ ID NO 98
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 98

gcttctgtgc cgtgccccgg 20

<210> SEQ ID NO 99
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 99

gcggcttctg tgccgtgccc 20

<210> SEQ ID NO 100
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 100

gcgcggcttc tgtgccgtgc 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

gggcgcggct tctgtgccgt 20

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

<400> SEQUENCE: 102

ggcggtgggc gcggcttctg 20

<210> SEQ ID NO 103

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<211> LENGTH: 20
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<400> SEQUENCE: 103

ggcaggcggt gggcgcggct 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

ctggcaggcg gtgggcgcgg 20

<210> SEQ ID NO 105
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 105

aactggcagg cggtgggcgc 20

<210> SEQ ID NO 106
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 106

gtgaactggc aggcggtggg 20

<210> SEQ ID NO 107
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 107

ggttgtgaac tggcaggcgg 20

<210> SEQ ID NO 108
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 108

gcggttgtga actggcaggc 20

<210> SEQ ID NO 109
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 109

cggagcggtt gtgaactggc 20

<210> SEQ ID NO 110
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 110

cgctcggagc ggttgtgaac 20

<210> SEQ ID NO 111
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 111

cccacgctcg gagcggttgt 20

<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 112

agacccacgc tcggagcggt 20

<210> SEQ ID NO 113
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 113

cggagaccca cgctcggagc 20

<210> SEQ ID NO 114
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 114

gggcggagac ccacgctcgg 20

<210> SEQ ID NO 115
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 115

gctgggcgga gacccacgct 20

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<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 116

ggagctgggc ggagacccac 20

<210> SEQ ID NO 117
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 117

ctggagctgg gcggagaccc 20

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 118

ggactggagc tgggcggaga 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

caggactgga gctgggcgga 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

atcacaggac tggagctggg 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

gggcgggccc ggatcacagg 20

<210> SEQ ID NO 122
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 122

ggggggcggc ccggatcaca 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

aggcagcacc atggcccctc 20

<210> SEQ ID NO 124
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 124

ggtccaacac cagctgctgg 20

<210> SEQ ID NO 125
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 125

cgatcacctt cagaatctcg 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

cttgttcatg atcttcatgg 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

ccccattcac caacacgtcc 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

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gcgtgatcca ccgccggtcc 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

gtaatactcc atgaccaggt 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

gcagtgtcag caggtccccg 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

caccgagtct atggccatga 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

acgtagccaa gccggtgcac 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

atgtggccac agcggtccag 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

cttcgtccac cagcggcaga 20

<210> SEQ ID NO 135
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 135

gacccttcg tccaccagcg 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

cctgctccac cccggcccag 20

<210> SEQ ID NO 137
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 137

cggaagtcgc ctgctccacc 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

cggagaccat cccagtcgag 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

tgagggccat gcaggagtag 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

ctccagttcc atgggtgtgg 20

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

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<400> SEQUENCE: 141

gcgcttgcac gtgtggctca 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

gccacttcag ctgtttcatc 20

<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 143

gcctcagcct ctgccgcagg 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

gcagcgtcac ctcggcctca 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

ggctcaggct ctgccgggtg 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

ttccgagcct ctgcctcgcg 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

ggtcccggtt ccgagcctct 20

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<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

atccgctcct gcaactgccg 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

gcaactccat ccgctcctgc 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

aggtggatcc gtggcccggg 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

cgcggcttct gtgccgtgcc 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

ttgctgcctt cccaggcctg 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

tgctcccgac aagctccaga 20

<210> SEQ ID NO 154
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 154

agaacctgcc cattgctgaa 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

cactgagggc cagacatatg 20

<210> SEQ ID NO 156
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 156

ctctagattc agatgcaggt 20

<210> SEQ ID NO 157
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 157

cgggccgtcc gtgtt 15

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

<400> SEQUENCE: 158

ctttgcactt tgcgaaccaa 20

<210> SEQ ID NO 159
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 159

catcctccac gcacccccac c 21

<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

gcctggcagc ccctgtccag 20

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<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

ggcctggcag cccctgtcca 20

<210> SEQ ID NO 162
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 162

gggcctggca gcccctgtcc 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

atggcccctc cccgggccgg 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

catggcccct ccccgggccg 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

ccatggcccc tccccgggcc 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

accatggccc ctccccgggc 20

<210> SEQ ID NO 167
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 167

caccatggcc cctccccggg 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

gcaccatggc ccctccccgg 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

agcaccatgg cccctccccg 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

cagcaccatg gcccctcccc 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

gcagcaccat ggcccctccc 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

ggcagcacca tggcccctcc 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

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caggcagcac catggcccct 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

acaggcagca ccatggcccc 20

<210> SEQ ID NO 175
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 175

ggacaggcag caccatggcc 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

tggacaggca gcaccatggc 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

ttggacaggc agcaccatgg 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

gttggacagg cagcaccatg 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

tgttggacag gcagcaccat 20

<210> SEQ ID NO 180

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

<400> SEQUENCE: 180

atgttggaca ggcagcacca 20

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<220> FEATURE:
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catgttggac aggcagcacc 20

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acatgttgga caggcagcac 20

<210> SEQ ID NO 183
<211> LENGTH: 20
<212> TYPE: DNA
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gacatgttgg acaggcagca 20

<210> SEQ ID NO 184
<211> LENGTH: 20
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tgacatgttg gacaggcagc 20

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<211> LENGTH: 20
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ctgacatgtt ggacaggcag 20

<210> SEQ ID NO 186
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<400> SEQUENCE: 186

gctgacatgt tggacaggca 20

<210> SEQ ID NO 187
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ggctgacatg ttggacaggc 20

<210> SEQ ID NO 188
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cggctgacat gttggacagg 20

<210> SEQ ID NO 189
<211> LENGTH: 20
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 189

tcggctgaca tgttggacag 20

<210> SEQ ID NO 190
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 190

ctcggctgac atgttggaca 20

<210> SEQ ID NO 191
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<400> SEQUENCE: 191

cctcggctga catgttggac 20

<210> SEQ ID NO 192
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acctcggctg acatgttgga 20

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<210> SEQ ID NO 193
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cacctcggct gacatgttgg 20

<210> SEQ ID NO 194
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gcacctcggc tgacatgttg 20

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cgcacctcgg ctgacatgtt 20

<210> SEQ ID NO 196
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<212> TYPE: DNA
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ccgcacctcg gctgacatgt 20

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<400> SEQUENCE: 197

gccgcacctc ggctgacatg 20

<210> SEQ ID NO 198
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<212> TYPE: DNA
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agccgcacct cggctgacat 20

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<220> FEATURE:
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cagccgcacc tcggctgaca 20

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tcagccgcac ctcggctgac 20

<210> SEQ ID NO 201
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<212> TYPE: DNA
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<400> SEQUENCE: 201

ctcagccgca cctcggctga 20

<210> SEQ ID NO 202
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 202

cctcagccgc acctcggctg 20

<210> SEQ ID NO 203
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 203

gcctcagccg cacctcggct 20

<210> SEQ ID NO 204
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 204

ccaacaccag ctgctggagc 20

<210> SEQ ID NO 205
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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tccaacacca gctgctggag 20

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gtccaacacc agctgctgga 20

<210> SEQ ID NO 207
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gggtccaaca ccagctgctg 20

<210> SEQ ID NO 208
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<400> SEQUENCE: 208

ggctccagcc ccaggaagcc 20

<210> SEQ ID NO 209
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 209

gggctccagc cccaggaagc 20

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

caggagaagg tcgagcaggg 20

<210> SEQ ID NO 211
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 211

cccaggagaa ggtcgagcag 20

<210> SEQ ID NO 212
<211> LENGTH: 20

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 212

gcccaggaga aggtcgagca 20

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

<400> SEQUENCE: 213

cgcccaggag aaggtcgagc 20

<210> SEQ ID NO 214
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 214

acgcccagga gaaggtcgag 20

<210> SEQ ID NO 215
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 215

tcctgggcca gttcggaggc 20

<210> SEQ ID NO 216
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 216

gtcctgggcc agttcggagg 20

<210> SEQ ID NO 217
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 217

tgtcctgggc cagttcggag 20

<210> SEQ ID NO 218
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 218

ttgtcctggg ccagttcgga 20

<210> SEQ ID NO 219
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 219

cttgtcctgg gccagttcgg 20

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

<400> SEQUENCE: 220

acttgtcctg ggccagttcg 20

<210> SEQ ID NO 221
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 221

tacttgtcct gggccagttc 20

<210> SEQ ID NO 222
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 222

gtacttgtcc tgggccagtt 20

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

<400> SEQUENCE: 223

cgtacttgtc ctgggccagt 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

actgcaagaa gtcggccacg 20

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<210> SEQ ID NO 225
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 225

ccactgcaag aagtcggcca 20

<210> SEQ ID NO 226
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 226

cccactgcaa gaagtcggcc 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

gcccactgca agaagtcggc 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

cgcccactgc aagaagtcgg 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

ccgcccactg caagaagtcg 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

tccgcccact gcaagaagtc 20

<210> SEQ ID NO 231
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 231

ctccgcccac tgcaagaagt 20

<210> SEQ ID NO 232
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 232

gctccgccca ctgcaagaag 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

ggctccgccc actgcaagaa 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

gggctccgcc cactgcaaga 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

tgggctccgc ccactgcaag 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

atgggctccg cccactgcaa 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

gatgggctcc gcccactgca 20

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<210> SEQ ID NO 238
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 238

cgatgggctc cgcccactgc 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

acgatgggct ccgcccactg 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

cacgatgggc tccgcccact 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

ccacgatggg ctccgcccac 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

accacgatgg gctccgccca 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

caccacgatg ggctccgccc 20

<210> SEQ ID NO 244
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 244

tcaccacgat gggctccgcc 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

ctcaccacga tgggctccgc 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

cctcaccacg atgggctccg 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

gcctcaccac gatgggctcc 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

agcctcacca cgatgggctc 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

aagcctcacc acgatgggct 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

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taagcctcac cacgatgggc 20

<210> SEQ ID NO 251
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 251

ttaagcctca ccacgatggg 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

cttaagcctc accacgatgg 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

ccttaagcct caccacgatg 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

tccttaagcc tcaccacgat 20

<210> SEQ ID NO 255
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 255

ctccttaagc ctcaccacga 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

cctccttaag cctcaccacg 20

<210> SEQ ID NO 257

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

<400> SEQUENCE: 257

acctccttaa gcctcaccac 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

gacctcctta agcctcacca 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

ggacctcctt aagcctcacc 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

cggacctcct taagcctcac 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

tcggacctcc ttaagcctca 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

gtcggacctc cttaagcctc 20

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

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<400> SEQUENCE: 263

cagtcggacc tccttaagcc 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

gcagtcggac ctccttaagc 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

tgcagtcgga cctccttaag 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

ccttcagaat ctcgaagtcg 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

accttcagaa tctcgaagtc 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

tcaccttcag aatctcgaag 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

atcaccttca gaatctcgaa 20

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<210> SEQ ID NO 270
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 270

gatcaccttc agaatctcga 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

ccgatcacct tcagaatctc 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

tccgatcacc ttcagaatct 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

gtccgatcac cttcagaatc 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

cgtccgatca ccttcagaat 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

cccgtctgct tcatcttcac 20

<210> SEQ ID NO 276
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 276

gcccgtctgc ttcatcttca 20

<210> SEQ ID NO 277
<211> LENGTH: 20
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ggcccgtctg cttcatcttc 20

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tggcccgtct gcttcatctt 20

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cacctggccc gtctgcttca 20

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ccacttgttc atgatcttca 20

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tcttcagcat gtcccacttg 20

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<210> SEQ ID NO 307
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<212> TYPE: DNA
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<400> SEQUENCE: 307

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<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 309

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<210> SEQ ID NO 310
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<210> SEQ ID NO 311
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<212> TYPE: DNA
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<400> SEQUENCE: 311

cacctcgccc ctcttcagca 20

<210> SEQ ID NO 312
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<212> TYPE: DNA
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<400> SEQUENCE: 312

acacctcgcc cctcttcagc 20

<210> SEQ ID NO 313
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<400> SEQUENCE: 313

gacacctcgc ccctcttcag 20

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<400> SEQUENCE: 314

gccaggcgga tgtggccaca 20

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accgcaccgt tccatctgcc 20

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<212> TYPE: DNA
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<400> SEQUENCE: 316

gaccgcaccg ttccatctgc 20

<210> SEQ ID NO 317
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<212> TYPE: DNA
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<400> SEQUENCE: 317

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<400> SEQUENCE: 318

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<212> TYPE: DNA
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<400> SEQUENCE: 319

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<400> SEQUENCE: 320

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<210> SEQ ID NO 321
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<400> SEQUENCE: 321

gcccacagcc tgcaggatct 20

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<400> SEQUENCE: 322

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<212> TYPE: DNA
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<400> SEQUENCE: 323

ccgcccacag cctgcaggat 20

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<212> TYPE: DNA
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<400> SEQUENCE: 324

accgcccaca gcctgcagga 20

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<212> TYPE: DNA
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<400> SEQUENCE: 325

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<210> SEQ ID NO 326
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<212> TYPE: DNA
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<400> SEQUENCE: 326

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<210> SEQ ID NO 327
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cccaccgccc acagcctgca 20

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<400> SEQUENCE: 328

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ggcccaccgc ccacagcctg 20

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<400> SEQUENCE: 330

aggcccaccg cccacagcct 20

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<212> TYPE: DNA
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<400> SEQUENCE: 331

caggcccacc gcccacagcc 20

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ccaggcccac cgcccacagc 20

<210> SEQ ID NO 333
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cccaggccca ccgcccacag 20

<210> SEQ ID NO 334

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<400> SEQUENCE: 334

tcccaggccc accgcccaca 20

<210> SEQ ID NO 335
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<210> SEQ ID NO 336
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<212> TYPE: DNA
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<400> SEQUENCE: 336

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<210> SEQ ID NO 337
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<212> TYPE: DNA
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<400> SEQUENCE: 337

ctgtcccagg cccaccgccc 20

<210> SEQ ID NO 338
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<212> TYPE: DNA
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<400> SEQUENCE: 338

cctgtcccag gcccaccgcc 20

<210> SEQ ID NO 339
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<212> TYPE: DNA
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<400> SEQUENCE: 339

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<210> SEQ ID NO 340
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tgcctgtccc aggcccaccg 20

<210> SEQ ID NO 341
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<212> TYPE: DNA
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<400> SEQUENCE: 341

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<210> SEQ ID NO 342
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<212> TYPE: DNA
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<400> SEQUENCE: 342

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<210> SEQ ID NO 343
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<212> TYPE: DNA
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<400> SEQUENCE: 343

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<210> SEQ ID NO 344
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<212> TYPE: DNA
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<400> SEQUENCE: 344

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<210> SEQ ID NO 345
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<212> TYPE: DNA
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<400> SEQUENCE: 345

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<210> SEQ ID NO 346
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 346

cgtagctgcc tgtcccaggc 20

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<212> TYPE: DNA
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<400> SEQUENCE: 347

ccgtagctgc ctgtcccagg 20

<210> SEQ ID NO 348
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 348

cccgtagctg cctgtcccag 20

<210> SEQ ID NO 349
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<212> TYPE: DNA
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<400> SEQUENCE: 349

gcccgtagct gcctgtccca 20

<210> SEQ ID NO 350
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<212> TYPE: DNA
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<400> SEQUENCE: 350

ggcccgtagc tgcctgtccc 20

<210> SEQ ID NO 351
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<212> TYPE: DNA
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<400> SEQUENCE: 351

tagaacattt cataggcgaa 20

<210> SEQ ID NO 352
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<212> TYPE: DNA
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<400> SEQUENCE: 352

tctccgccgt ggaatccgcg 20

<210> SEQ ID NO 353
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 353

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

<400> SEQUENCE: 354

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<210> SEQ ID NO 355
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<212> TYPE: DNA
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<400> SEQUENCE: 355

aggtctccgc cgtggaatcc 20

<210> SEQ ID NO 356
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<212> TYPE: DNA
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<400> SEQUENCE: 356

taggtctccg ccgtggaatc 20

<210> SEQ ID NO 357
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<212> TYPE: DNA
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ttgtagtgga cgatcttgcc 20

<210> SEQ ID NO 358
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<212> TYPE: DNA
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cttgtagtgg acgatcttgc 20

<210> SEQ ID NO 359
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<400> SEQUENCE: 359

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ccttgtagtg gacgatcttg 20

<210> SEQ ID NO 360
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tccttgtagt ggacgatctt 20

<210> SEQ ID NO 361
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<212> TYPE: DNA
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<400> SEQUENCE: 361

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<210> SEQ ID NO 362
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 362

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<210> SEQ ID NO 363
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<212> TYPE: DNA
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<400> SEQUENCE: 363

tgctccttgt agtggacgat 20

<210> SEQ ID NO 364
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 364

gtgctccttg tagtggacga 20

<210> SEQ ID NO 365
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 365

ggtgctcctt gtagtggacg 20

<210> SEQ ID NO 366
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<212> TYPE: DNA
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aggtgctcct tgtagtggac 20

<210> SEQ ID NO 367
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<212> TYPE: DNA
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<400> SEQUENCE: 367

gaggtgctcc ttgtagtgga 20

<210> SEQ ID NO 368
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 368

agaggtgctc cttgtagtgg 20

<210> SEQ ID NO 369
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<212> TYPE: DNA
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<210> SEQ ID NO 370
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agagaggtgc tccttgtagt 20

<210> SEQ ID NO 371
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

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gagagaggtg ctccttgtag 20

<210> SEQ ID NO 372
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<400> SEQUENCE: 372

agagagaggt gctccttgta 20

<210> SEQ ID NO 373
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<400> SEQUENCE: 373

cagagagagg tgctccttgt 20

<210> SEQ ID NO 374
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<220> FEATURE:
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<400> SEQUENCE: 374

ggcagagaga ggtgctcctt 20

<210> SEQ ID NO 375
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 375

cggcagagag aggtgctcct 20

<210> SEQ ID NO 376
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 376

gcggcagaga gaggtgctcc 20

<210> SEQ ID NO 377
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 377

agcggcagag agaggtgctc 20

<210> SEQ ID NO 378
<211> LENGTH: 20
<212> TYPE: DNA
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cagcggcaga gagaggtgct 20

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ccagcggcag agagaggtgc 20

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ggcccagccg tgtctccggg 20

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cggcccagcc gtgtctccgg 20

<210> SEQ ID NO 382
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ccggcccagc cgtgtctccg 20

<210> SEQ ID NO 383
<211> LENGTH: 20
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cccggcccag ccgtgtctcc 20

<210> SEQ ID NO 384
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ccccggccca gccgtgtctc 20

<210> SEQ ID NO 385
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<223> OTHER INFORMATION: Synthetic oligonucleotide

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accccggccc agccgtgtct 20

<210> SEQ ID NO 386
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caccccggcc cagccgtgtc 20

<210> SEQ ID NO 387
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 387

ccaccccggc ccagccgtgt 20

<210> SEQ ID NO 388
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tccaccccgg cccagccgtg 20

<210> SEQ ID NO 389
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ctccaccccg gcccagccgt 20

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gctccacccc ggcccagccg 20

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tgctccaccc cggcccagcc 20

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ctgctccacc ccggcccagc 20

<210> SEQ ID NO 393
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<212> TYPE: DNA
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aagggatgtg tccggaagtc 20

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

<400> SEQUENCE: 394

gaagggatgt gtccggaagt 20

<210> SEQ ID NO 395
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 395

agaagggatg tgtccggaag 20

<210> SEQ ID NO 396
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 396

aagaagggat gtgtccggaa 20

<210> SEQ ID NO 397
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 397

gaagaaggga tgtgtccgga 20

<210> SEQ ID NO 398
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 398

agaagaaggg atgtgtccgg 20

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<400> SEQUENCE: 399

aagaagaagg gatgtgtccg 20

<210> SEQ ID NO 400
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 400

aaagaagaag ggatgtgtcc 20

<210> SEQ ID NO 401
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 401

caaagaagaa gggatgtgtc 20

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<212> TYPE: DNA
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<400> SEQUENCE: 402

ccaaagaaga agggatgtgt 20

<210> SEQ ID NO 403
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 403

ggccaaagaa gaagggatgt 20

<210> SEQ ID NO 404
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 404

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aggccaaaga agaagggatg 20

<210> SEQ ID NO 405
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 405

gaggccaaag aagaagggat 20

<210> SEQ ID NO 406
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 406

cgaggccaaa gaagaaggga 20

<210> SEQ ID NO 407
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 407

tcgaggccaa agaagaaggg 20

<210> SEQ ID NO 408
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 408

gtcgaggcca aagaagaagg 20

<210> SEQ ID NO 409
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 409

agtcgaggcc aaagaagaag 20

<210> SEQ ID NO 410
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 410

cagtcgaggc caaagaagaa 20

<210> SEQ ID NO 411

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<211> LENGTH: 20
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 411

ccagtcgagg ccaaagaaga 20

<210> SEQ ID NO 412
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 412

cccagtcgag gccaaagaag 20

<210> SEQ ID NO 413
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 413

tcccagtcga ggccaaagaa 20

<210> SEQ ID NO 414
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 414

atcccagtcg aggccaaaga 20

<210> SEQ ID NO 415
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 415

catcccagtc gaggccaaag 20

<210> SEQ ID NO 416
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 416

ccatcccagt cgaggccaaa 20

<210> SEQ ID NO 417
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 417

accatcccag tcgaggccaa 20

<210> SEQ ID NO 418
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 418

gaccatccca gtcgaggcca 20

<210> SEQ ID NO 419
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 419

agaccatccc agtcgaggcc 20

<210> SEQ ID NO 420
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 420

gagaccatcc cagtcgaggc 20

<210> SEQ ID NO 421
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 421

ggagaccatc ccagtcgagg 20

<210> SEQ ID NO 422
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 422

ttcgaaatcc ggtgtaaagg 20

<210> SEQ ID NO 423
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 423

cttcgaaatc cggtgtaaag 20

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<210> SEQ ID NO 424
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 424

ccttcgaaat ccggtgtaaa 20

<210> SEQ ID NO 425
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 425

accttcgaaa tccggtgtaa 20

<210> SEQ ID NO 426
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 426

caccttcgaa atccggtgta 20

<210> SEQ ID NO 427
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 427

gcaccttcga aatccggtgt 20

<210> SEQ ID NO 428
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 428

ggcaccttcg aaatccggtg 20

<210> SEQ ID NO 429
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 429

tggcaccttc gaaatccggt 20

<210> SEQ ID NO 430
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 430

gtggcacctt cgaaatccgg 20

<210> SEQ ID NO 431
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 431

ggtggcacct tcgaaatccg 20

<210> SEQ ID NO 432
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 432

cggtggcacc ttcgaaatcc 20

<210> SEQ ID NO 433
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 433

tcggtggcac cttcgaaatc 20

<210> SEQ ID NO 434
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 434

gtcggtggca ccttcgaaat 20

<210> SEQ ID NO 435
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 435

tgtcggtggc accttcgaaa 20

<210> SEQ ID NO 436
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 436

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gtgtcggtgg caccttcgaa 20

<210> SEQ ID NO 437
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 437

tgtgtcggtg gcaccttcga 20

<210> SEQ ID NO 438
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 438

atgtgtcggt ggcaccttcg 20

<210> SEQ ID NO 439
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 439

catgtgtcgg tggcaccttc 20

<210> SEQ ID NO 440
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 440

gcatgtgtcg gtggcacctt 20

<210> SEQ ID NO 441
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 441

tgcatgtgtc ggtggcacct 20

<210> SEQ ID NO 442
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 442

ttgcatgtgt cggtggcacc 20

<210> SEQ ID NO 443
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 443

gttgcatgtg tcggtggcac 20

<210> SEQ ID NO 444
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 444

agttgcatgt gtcggtggca 20

<210> SEQ ID NO 445
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 445

aagttgcatg tgtcggtggc 20

<210> SEQ ID NO 446
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 446

gaagttgcat gtgtcggtgg 20

<210> SEQ ID NO 447
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 447

cgaagttgca tgtgtcggtg 20

<210> SEQ ID NO 448
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 448

gtcgaagttg catgtgtcgg 20

<210> SEQ ID NO 449
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 449

agtcgaagtt gcatgtgtcg 20

<210> SEQ ID NO 450
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 450

aagtcgaagt tgcatgtgtc 20

<210> SEQ ID NO 451
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 451

caagtcgaag ttgcatgtgt 20

<210> SEQ ID NO 452
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 452

ccaagtcgaa gttgcatgtg 20

<210> SEQ ID NO 453
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 453

accaagtcga agttgcatgt 20

<210> SEQ ID NO 454
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 454

caccaagtcg aagttgcatg 20

<210> SEQ ID NO 455
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 455

ccaccaagtc gaagttgcat 20

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<210> SEQ ID NO 456
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 456

tccaccaagt cgaagttgca 20

<210> SEQ ID NO 457
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 457

ctccaccaag tcgaagttgc 20

<210> SEQ ID NO 458
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 458

cctccaccaa gtcgaagttg 20

<210> SEQ ID NO 459
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 459

tcctccacca agtcgaagtt 20

<210> SEQ ID NO 460
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 460

gtcctccacc aagtcgaagt 20

<210> SEQ ID NO 461
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 461

cgtcctccac caagtcgaag 20

<210> SEQ ID NO 462
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 462

ccgtcctcca ccaagtcgaa 20

<210> SEQ ID NO 463
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 463

cccgtcctcc accaagtcga 20

<210> SEQ ID NO 464
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 464

gcccgtcctc caccaagtcg 20

<210> SEQ ID NO 465
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 465

agcccgtcct ccaccaagtc 20

<210> SEQ ID NO 466
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 466

gagcccgtcc tccaccaagt 20

<210> SEQ ID NO 467
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 467

tgagcccgtc ctccaccaag 20

<210> SEQ ID NO 468
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 468

ggttccgagc ctctgcctcg 20

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<210> SEQ ID NO 469
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 469

cggttccgag cctctgcctc 20

<210> SEQ ID NO 470
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 470

ccggttccga gcctctgcct 20

<210> SEQ ID NO 471
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 471

cccggttccg agcctctgcc 20

<210> SEQ ID NO 472
<211> LENGTH: 20
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<213> ORGANISM: Artificial Sequence
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tcccggttcc gagcctctgc 20

<210> SEQ ID NO 473
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<212> TYPE: DNA
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gtcccggttc cgagcctctg 20

<210> SEQ ID NO 474
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aggtcccggt tccgagcctc 20

<210> SEQ ID NO 475
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<213> ORGANISM: Artificial Sequence
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taggtcccgg ttccgagcct 20

<210> SEQ ID NO 476
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<213> ORGANISM: Artificial Sequence
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ctaggtcccg gttccgagcc 20

<210> SEQ ID NO 477
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tctaggtccc ggttccgagc 20

<210> SEQ ID NO 478
<211> LENGTH: 20
<212> TYPE: DNA
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ctctaggtcc cggttccgag 20

<210> SEQ ID NO 479
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<212> TYPE: DNA
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cctctaggtc ccggttccga 20

<210> SEQ ID NO 480
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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gcctctaggt cccggttccg 20

<210> SEQ ID NO 481
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catccgctcc tgcaactgcc 20

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ccatccgctc ctgcaactgc 20

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ctccatccgc tcctgcaact 20

<210> SEQ ID NO 485
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actccatccg ctcctgcaac 20

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aactccatcc gctcctgcaa 20

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caactccatc cgctcctgca 20

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agcaactcca tccgctcctg 20

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cagcaactcc atccgctcct 20

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gcagcaactc catccgctcc 20

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cagctgtggc tccctctgcc 20

<210> SEQ ID NO 492
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acagctgtgg ctccctctgc 20

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gacagctgtg gctccctctg 20

<210> SEQ ID NO 494
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<400> SEQUENCE: 494

tgacagctgt ggctccctct 20

<210> SEQ ID NO 495
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gtgacagctg tggctccctc 20

<210> SEQ ID NO 496
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<212> TYPE: DNA
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cgtgacagct gtggctccct 20

<210> SEQ ID NO 497
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<212> TYPE: DNA
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<400> SEQUENCE: 497

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<210> SEQ ID NO 498
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 498

cccgtgacag ctgtggctcc 20

<210> SEQ ID NO 499
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 499

ccccgtgaca gctgtggctc 20

<210> SEQ ID NO 500
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 500

cccccgtgac agctgtggct 20

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

<400> SEQUENCE: 501

accccgtga cagctgtggc 20

<210> SEQ ID NO 502
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 502

gacccccgtg acagctgtgg 20

<210> SEQ ID NO 503
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 503

ggacccccgt gacagctgtg 20

<210> SEQ ID NO 504
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 504

gggacccccg tgacagctgt 20

<210> SEQ ID NO 505
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 505

gaaggtggat ccgtggcccg 20

<210> SEQ ID NO 506
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 506

ggaaggtgga tccgtggccc 20

<210> SEQ ID NO 507
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 507

gggaaggtgg atccgtggcc 20

<210> SEQ ID NO 508
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 508

tgggaaggtg gatccgtggc 20

<210> SEQ ID NO 509
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 509

atgggaaggt ggatccgtgg 20

<210> SEQ ID NO 510
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 510

gatgggaagg tggatccgtg 20

<210> SEQ ID NO 511
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 511

tagatgggaa ggtggatccg 20

<210> SEQ ID NO 512
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 512

ctagatggga aggtggatcc 20

<210> SEQ ID NO 513
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 513

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tctagatggg aaggtggatc 20

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

<400> SEQUENCE: 514

atctagatgg gaaggtggat 20

<210> SEQ ID NO 515
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 515

ccatctagat gggaaggtgg 20

<210> SEQ ID NO 516
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 516

gccatctaga tgggaaggtg 20

<210> SEQ ID NO 517
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 517

ggccatctag atgggaaggt 20

<210> SEQ ID NO 518
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 518

caccagcggg cactggccca 20

<210> SEQ ID NO 519
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 519

ccaccagcgg gcactggccc 20

<210> SEQ ID NO 520
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 520

cccaccagcg ggcactggcc 20

<210> SEQ ID NO 521
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 521

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<210> SEQ ID NO 522
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 522

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<210> SEQ ID NO 523
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 523

tggccccacc agcgggcact 20

<210> SEQ ID NO 524
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 524

ctggccccac cagcgggcac 20

<210> SEQ ID NO 525
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 525

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<210> SEQ ID NO 526
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<212> TYPE: DNA
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<400> SEQUENCE: 526

gcctggcccc accagcgggc 20

<210> SEQ ID NO 527
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 527

gggcctggcc ccaccagcgg 20

<210> SEQ ID NO 528
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 528

aggtggcggc ggtgcatggg 20

<210> SEQ ID NO 529
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 529

caggtggcgg cggtgcatgg 20

<210> SEQ ID NO 530
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 530

gcaggtggcg gcggtgcatg 20

<210> SEQ ID NO 531
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 531

agcaggtggc ggcggtgcat 20

<210> SEQ ID NO 532
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 532

cagcaggtgg cggcggtgca 20

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<210> SEQ ID NO 533
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 533

gcagcaggtg gcggcggtgc 20

<210> SEQ ID NO 534
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 534

agcagcaggt ggcggcggtg 20

<210> SEQ ID NO 535
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 535

gagcagcagg tggcggcggt 20

<210> SEQ ID NO 536
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 536

ggagcagcag gtggcggcgg 20

<210> SEQ ID NO 537
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 537

gggagcagca ggtggcggcg 20

<210> SEQ ID NO 538
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 538

agggagcagc aggtggcggc 20

<210> SEQ ID NO 539
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 539

cagggagcag caggtggcgg 20

<210> SEQ ID NO 540
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 540

gcagggagca gcaggtggcg 20

<210> SEQ ID NO 541
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 541

ggcagggagc agcaggtggc 20

<210> SEQ ID NO 542
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 542

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<210> SEQ ID NO 543
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 543

ctggcaggga gcagcaggtg 20

<210> SEQ ID NO 544
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 544

ccctggcagg gagcagcagg 20

<210> SEQ ID NO 545
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 545

accctggcag ggagcagcag 20

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<210> SEQ ID NO 546
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 546

gaccctggca gggagcagca 20

<210> SEQ ID NO 547
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 547

ggaccctggc agggagcagc 20

<210> SEQ ID NO 548
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 548

ggcctaggga ccctggcagg 20

<210> SEQ ID NO 549
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 549

aggcctaggg accctggcag 20

<210> SEQ ID NO 550
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 550

ccaggcctag ggaccctggc 20

<210> SEQ ID NO 551
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 551

gccaggccta gggaccctgg 20

<210> SEQ ID NO 552
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 552

ggccaggcct agggaccctg 20

<210> SEQ ID NO 553
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 553

aggccaggcc tagggaccct 20

<210> SEQ ID NO 554
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 554

taggccaggc ctagggaccc 20

<210> SEQ ID NO 555
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 555

ataggccagg cctagggacc 20

<210> SEQ ID NO 556
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 556

gataggccag gcctagggac 20

<210> SEQ ID NO 557
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 557

cgataggcca ggcctaggga 20

<210> SEQ ID NO 558
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 558

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ccgataggcc aggcctaggg 20

<210> SEQ ID NO 559
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 559

tccgataggc caggcctagg 20

<210> SEQ ID NO 560
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 560

ctccgatagg ccaggcctag 20

<210> SEQ ID NO 561
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 561

cctccgatag gccaggccta 20

<210> SEQ ID NO 562
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 562

gcctccgata ggccaggcct 20

<210> SEQ ID NO 563
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 563

gcgcctccga taggccaggc 20

<210> SEQ ID NO 564
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 564

aacaggagca gggaaagcgc 20

<210> SEQ ID NO 565

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

<400> SEQUENCE: 565

gaacaggagc agggaaagcg 20

<210> SEQ ID NO 566
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 566

cgaacaggag cagggaaagc 20

<210> SEQ ID NO 567
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 567

gcgaacagga gcagggaaag 20

<210> SEQ ID NO 568
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 568

ggcgaacagg agcagggaaa 20

<210> SEQ ID NO 569
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 569

cggcgaacag gagcagggaa 20

<210> SEQ ID NO 570
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 570

acggcgaaca ggagcaggga 20

<210> SEQ ID NO 571
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 571

aacggcgaac aggagcaggg 20

<210> SEQ ID NO 572
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 572

caacggcgaa caggagcagg 20

<210> SEQ ID NO 573
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 573

gggcggcggc acgagacaga 20

<210> SEQ ID NO 574
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 574

agggcggcgg cacgagacag 20

<210> SEQ ID NO 575
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 575

cagggcggcg gcacgagaca 20

<210> SEQ ID NO 576
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 576

ccagggcggc ggcacgagac 20

<210> SEQ ID NO 577
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 577

cccagggcgg cggcacgaga 20

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<210> SEQ ID NO 578
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 578

gcccagggcg gcggcacgag 20

<210> SEQ ID NO 579
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 579

agcccagggc ggcggcacga 20

<210> SEQ ID NO 580
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 580

cagcccaggg cggcggcacg 20

<210> SEQ ID NO 581
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 581

gcagcccagg gcggcggcac 20

<210> SEQ ID NO 582
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 582

ctgcggtgag ttggccggcg 20

<210> SEQ ID NO 583
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 583

actgcggtga gttggccggc 20

<210> SEQ ID NO 584
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 584

gactgcggtg agttggccgg 20

<210> SEQ ID NO 585
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 585

agactgcggt gagttggccg 20

<210> SEQ ID NO 586
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 586

cagactgcgg tgagttggcc 20

<210> SEQ ID NO 587
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 587

ccagactgcg gtgagttggc 20

<210> SEQ ID NO 588
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 588

gccagactgc ggtgagttgg 20

<210> SEQ ID NO 589
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 589

cgccagactg cggtgagttg 20

<210> SEQ ID NO 590
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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aagacagttc tagggttcag 20

<210> SEQ ID NO 591
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 591

gaagacagtt ctagggttca 20

<210> SEQ ID NO 592
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 592

cgaagacagt tctagggttc 20

<210> SEQ ID NO 593
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 593

tcgaagacag ttctagggtt 20

<210> SEQ ID NO 594
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 594

gtcgaagaca gttctagggt 20

<210> SEQ ID NO 595
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 595

agtcgaagac agttctaggg 20

<210> SEQ ID NO 596
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 596

gagtcgaaga cagttctagg 20

<210> SEQ ID NO 597
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 597

ggagtcgaag acagttctag 20

<210> SEQ ID NO 598
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 598

cggagtcgaa gacagttcta 20

<210> SEQ ID NO 599
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 599

ccggagtcga agacagttct 20

<210> SEQ ID NO 600
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 600

cccggagtcg aagacagttc 20

<210> SEQ ID NO 601
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 601

ccccggagtc gaagacagtt 20

<210> SEQ ID NO 602
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 602

gccccggagt cgaagacagt 20

<210> SEQ ID NO 603
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 603

ggccccggag tcgaagacag 20

<210> SEQ ID NO 604
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 604

gggccccgga gtcgaagaca 20

<210> SEQ ID NO 605
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 605

aggcggtggg cgcggcttct 20

<210> SEQ ID NO 606
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 606

caggcggtgg gcgcggcttc 20

<210> SEQ ID NO 607
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 607

gcaggcggtg ggcgcggctt 20

<210> SEQ ID NO 608
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 608

tggcaggcgg tgggcgcggc 20

<210> SEQ ID NO 609
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 609

actggcaggc ggtgggcgcg 20

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<210> SEQ ID NO 610
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 610

gaactggcag gcggtgggcg 20

<210> SEQ ID NO 611
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 611

tgaactggca ggcggtgggc 20

<210> SEQ ID NO 612
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 612

tgtgaactgg caggcggtgg 20

<210> SEQ ID NO 613
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 613

tggagctggg cggagaccca 20

<210> SEQ ID NO 614
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 614

actggagctg ggcggagacc 20

<210> SEQ ID NO 615
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 615

gactggagct gggcggagac 20

<210> SEQ ID NO 616
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 616

aggactggag ctgggcggag 20

<210> SEQ ID NO 617
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 617

acaggactgg agctgggcgg 20

<210> SEQ ID NO 618
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 618

cacaggactg gagctgggcg 20

<210> SEQ ID NO 619
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 619

tcacaggact ggagctgggc 20

<210> SEQ ID NO 620
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 620

gcctcagcct ggccgaaaga 20

<210> SEQ ID NO 621
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 621

ggcctcagcc tggccgaaag 20

<210> SEQ ID NO 622
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 622

tggtggagcc aagccctccc 20

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<210> SEQ ID NO 623
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 623

gggcaccctc agagcctgaa 20

<210> SEQ ID NO 624
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 624

accccactgc aagaagtcgg 20

<210> SEQ ID NO 625
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 625

gccccaggat gggaggatct 20

<210> SEQ ID NO 626
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 626

cataggacag agaaatgttg 20

<210> SEQ ID NO 627
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 627

tgctgacctt actctgcccc 20

<210> SEQ ID NO 628
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 628

taagccatgg ctctgagtca 20

<210> SEQ ID NO 629
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 629

agagaggcca tgggaggctg 20

<210> SEQ ID NO 630
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 630

ctggccctcc tggcttgccc 20

<210> SEQ ID NO 631
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 631

agctgcccca tgctggccct 20

<210> SEQ ID NO 632
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 632

gcccctggca gctgccccat 20

<210> SEQ ID NO 633
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 633

ctgtcggctg cgcccctggc 20

<210> SEQ ID NO 634
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 634

cgccgaacac ctgcctgtcg 20

<210> SEQ ID NO 635
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 635

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cctcccagtg cctgggcacc 20

<210> SEQ ID NO 636
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 636

gcgcctgtct gcaaagctgg 20

<210> SEQ ID NO 637
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 637

cccaaagttg tccctcctgg 20

<210> SEQ ID NO 638
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 638

acacccagaa gaacccaaag 20

<210> SEQ ID NO 639
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 639

ctgacccaca cggctcatag 20

<210> SEQ ID NO 640
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 640

tggccccagg ccctggaaag 20

<210> SEQ ID NO 641
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 641

gacaaggcag ctggcagaag 20

<210> SEQ ID NO 642

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

<400> SEQUENCE: 642

aagaaaccag tgaccagtga 20

<210> SEQ ID NO 643
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 643

ctgtgaaatg ggaggaggag 20

<210> SEQ ID NO 644
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 644

gaaggttttt ccagaggctg 20

<210> SEQ ID NO 645
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 645

ggccaggaga gtcattaggg 20

<210> SEQ ID NO 646
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 646

ccacaaaagg agtgctcctc 20

<210> SEQ ID NO 647
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 647

ccttttaagg cagcaggaac 20

<210> SEQ ID NO 648
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 648

ctaggactgt ctgcttccca 20

<210> SEQ ID NO 649
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 649

gtcattcatc aatttctaag 20

<210> SEQ ID NO 650
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 650

ggaggagctg cagccggaga 20

<210> SEQ ID NO 651
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 651

gcacccggag gagctgcagc 20

<210> SEQ ID NO 652
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 652

gcacgacacc tgcagggcac 20

<210> SEQ ID NO 653
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 653

agctcaccag gtagttctca 20

<210> SEQ ID NO 654
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 654

gcttcctctc cccacctcct 20

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<210> SEQ ID NO 655
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 655

gcagcacccc caatcctaga 20

<210> SEQ ID NO 656
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 656

gcccctcatc cacctgacac 20

<210> SEQ ID NO 657
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 657

ttccaggtaa gagacccccc 20

<210> SEQ ID NO 658
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 658

agaataggtc ccagacactc 20

<210> SEQ ID NO 659
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 659

ctccccctga gatgttctgg 20

<210> SEQ ID NO 660
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 660

ccccagccca gagataacca 20

<210> SEQ ID NO 661
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 661

cctgatccat cacggatggc 20

<210> SEQ ID NO 662
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 662

tactccatga ccaggtactg 20

<210> SEQ ID NO 663
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 663

gctctgacct tccaagaacc 20

<210> SEQ ID NO 664
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 664

ctcccttctg tggtcccacc 20

<210> SEQ ID NO 665
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 665

gtcgggtttg atgtccctgc 20

<210> SEQ ID NO 666
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 666

agggcactgg ctcaccgttc 20

<210> SEQ ID NO 667
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 667

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gggccctcct tccaaccact 20

<210> SEQ ID NO 668
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 668

gcccaccct ctgggcccac 20

<210> SEQ ID NO 669
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 669

aggagcagag cgaggcttgg 20

<210> SEQ ID NO 670
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 670

caccttgtag tggacgatct 20

<210> SEQ ID NO 671
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 671

ctaccccgcc cccgctcacc 20

<210> SEQ ID NO 672
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 672

ctaggtcact gctgggtcct 20

<210> SEQ ID NO 673
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 673

ctcagatagc tccccactcc 20

<210> SEQ ID NO 674
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 674

aattctctaa ttctctagac 20

<210> SEQ ID NO 675
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 675

tacctgaggg ccatgcagga 20

<210> SEQ ID NO 676
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 676

gttccaagac tgatcctgca 20

<210> SEQ ID NO 677
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 677

aggagggcgg tggcgcggcg 20

<210> SEQ ID NO 678
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 678

tgacagctgg aaggagaaga 20

<210> SEQ ID NO 679
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 679

catgggaagg tggatccgtg 20

<210> SEQ ID NO 680
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 680

ggaggttatc tagggagatc 20

<210> SEQ ID NO 681
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 681

gaagggacag gtgacccgat 20

<210> SEQ ID NO 682
<211> LENGTH: 20
<212> TYPE: DNA
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cgtaccctgg cagggagcag 20

<210> SEQ ID NO 683
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 683

ggactcgccc cgcctacgcc 20

<210> SEQ ID NO 684
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 684

ctcctgggac tcgccccgcc 20

<210> SEQ ID NO 685
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 685

gctcctggga ctcgccccgc 20

<210> SEQ ID NO 686
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 686

attggctcct gggactcgcc 20

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<210> SEQ ID NO 687
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 687

gattggctcc tgggactcgc 20

<210> SEQ ID NO 688
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 688

gcctctgatt ggctcctggg 20

<210> SEQ ID NO 689
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 689

gcatgggcct ctgattggct 20

<210> SEQ ID NO 690
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 690

cacccggcat gggcctctga 20

<210> SEQ ID NO 691
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 691

gccaggccta gggacctgcg 20

<210> SEQ ID NO 692
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 692

ttcctccccc aaccctgatt 20

<210> SEQ ID NO 693
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 693

aagtttgcag caacttttct 20

<210> SEQ ID NO 694
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 694

gcccctcgga attcccggct 20

<210> SEQ ID NO 695
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 695

catctcggcc tgcgctccgc 20

<210> SEQ ID NO 696
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 696

gcaggccccc acattcccca 20

<210> SEQ ID NO 697
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 697

cttctgcacg cctccgtctc 20

<210> SEQ ID NO 698
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 698

tggcccacag ccacggccgg 20

<210> SEQ ID NO 699
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 699

ggcctggccc caccagcggg 20

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<210> SEQ ID NO 700
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 700

cctggcaggg agcagcaggt 20

<210> SEQ ID NO 701
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 701

cagccgcact tcggctgaca 20

<210> SEQ ID NO 702
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 702

gcctgggtcc agcaccagct 20

<210> SEQ ID NO 703
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 703

gtcccaggaa gcctgggtcc 20

<210> SEQ ID NO 704
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 704

cgttagcagg tccccgccca 20

<210> SEQ ID NO 705
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 705

gtctatggcc atgacaatct 20

<210> SEQ ID NO 706
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 706

gtagcccagc cggtgcacgg 20

<210> SEQ ID NO 707
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 707

gggtgcccac agccaccagc 20

<210> SEQ ID NO 708
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 708

tggcccgtag ctgcctgccc 20

<210> SEQ ID NO 709
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 709

ggaaatcacc tgccccacct 20

<210> SEQ ID NO 710
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 710

ggatgtttct ggaaatcacc 20

<210> SEQ ID NO 711
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 711

gtggcaccct cgaagtctgg 20

<210> SEQ ID NO 712
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 712

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ccccgctcac catggcagtg 20

<210> SEQ ID NO 713
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 713

ggtccgggac ctgattgtct 20

<210> SEQ ID NO 714
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 714

gctgcatgtc tgcccgtccc 20

<210> SEQ ID NO 715
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 715

ggccccagaa ccctagctgc 20

<210> SEQ ID NO 716
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 716

tcacagggcc tggctgcccc 20

<210> SEQ ID NO 717
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 717

ggctgacatg ttgggcaggc 20

<210> SEQ ID NO 718
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 718

tgtccaggcc ccagaaccct 20

<210> SEQ ID NO 719

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

<400> SEQUENCE: 719

ggccaggcct agggatctgc 20

<210> SEQ ID NO 720
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 720

cgcctcggat aggccaggcc 20

<210> SEQ ID NO 721
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 721

ggcttggagt cttagggttc 20

<210> SEQ ID NO 722
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 722

tccccggccg ccaggtggca 20

<210> SEQ ID NO 723
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 723

ggtgctgggc acgagccctg 20

<210> SEQ ID NO 724
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 724

gcccagctgc tgcagcagcg 20

<210> SEQ ID NO 725
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 725

ccgtgtgtgc tggcagaggt 20

<210> SEQ ID NO 726
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 726

ataaataccg aggaatgtcg 20

<210> SEQ ID NO 727
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 727

gggacagaca ataaataccg 20

<210> SEQ ID NO 728
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 728

gtgcagccca gtgtggcggc 20

<210> SEQ ID NO 729
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 729

cctggagaag ttctggttgg 20

<210> SEQ ID NO 730
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 730

ggtgacccga tcggagccca 20

<210> SEQ ID NO 731
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 731

agctggagag agaagggaca 20

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<210> SEQ ID NO 732
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 732

gtgagggact cgcctgcggc 20

<210> SEQ ID NO 733
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 733

gcggctgcgg tgccccagcc 20

<210> SEQ ID NO 734
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 734

gggccatcta gctggagaga 20

<210> SEQ ID NO 735
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 735

ccccactgca agaagtcggc 20

<210> SEQ ID NO 736
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 736

ttgagccctt ttaaggcagc 20

<210> SEQ ID NO 737
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 737

tgaccaggta ctgggagcgg 20

<210> SEQ ID NO 738
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 738

cctggagctg gatcagtccc 20

<210> SEQ ID NO 739
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 739

acatgggaag gtggatccgt 20

<210> SEQ ID NO 740
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 740

gtgggacata ccctggcagg 20

<210> SEQ ID NO 741
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 741

gccaggccta gggatctgca 20

<210> SEQ ID NO 742
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 742

ggaagcacga cacctcgcct 20

<210> SEQ ID NO 743
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 743

cctcaccatt ccatcaggct 20

<210> SEQ ID NO 744
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 744

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cggcagcgac aagtgttccc 20

<210> SEQ ID NO 745
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 745

gtctctgaag gccatgcagc 20

<210> SEQ ID NO 746
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 746

cagccacttg atccggtggg 20

<210> SEQ ID NO 747
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 747

aggtcggcct cttcagccac 20

<210> SEQ ID NO 748
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 748

gttggctgga gaagttctgg 20

<210> SEQ ID NO 749
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 749

ccccgtgatg gctgcggctc 20

<210> SEQ ID NO 750
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 750

aggccaggcc tagggatcct 20

<210> SEQ ID NO 751
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 751

ggcgcggtgc cccagcctgg 20

<210> SEQ ID NO 752
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 752

gtcctggccc caccagcggg 20

<210> SEQ ID NO 753
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 753

ccaggcctag gaatcctggc 20

<210> SEQ ID NO 754
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 754

gcgcctcgga tagccaggcc 20

<210> SEQ ID NO 755
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 755

cccagtgtgg cgcagcagcc 20

<210> SEQ ID NO 756
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 756

gtgtttcatc ttcaccaccg 20

<210> SEQ ID NO 757
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 757

aggtcagcct cttcagccac 20

<210> SEQ ID NO 758
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 758

ggccatatgg gaaggtggat 20

<210> SEQ ID NO 759
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 759

ggaggatttg gcgagaagca 20

<210> SEQ ID NO 760
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 760

cgaagtctgc cccacctcga 20

<210> SEQ ID NO 761
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 761

gtggcaccct cgaagtctgc 20

<210> SEQ ID NO 762
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 762

gggtccattg taaggaagct 20

<210> SEQ ID NO 763
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 763

ggtgcccaca gccaccaggg 20

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<210> SEQ ID NO 764
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 764

tccatggcag tgagccggtc 20

<210> SEQ ID NO 765
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 765

gggaccactt gatccggtgg 20

<210> SEQ ID NO 766
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 766

ggatcagagt tgggaccact 20

<210> SEQ ID NO 767
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 767

ccccgtgatg gctgcggttc 20

<210> SEQ ID NO 768
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 768

gtgtgtcctc ataccccgcc 20

<210> SEQ ID NO 769
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 769

gcaccctcga agtctcgacc 20

<210> SEQ ID NO 770
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 770

gctctgaagg ccatgcagca 20

<210> SEQ ID NO 771
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 771

gacatatgcc aagattgtgc actac 25

<210> SEQ ID NO 772
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 772

cacgaatgag gtcctgagct t 21

<210> SEQ ID NO 773
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 773

aacacttgtc gctgccgctg gc 22

<210> SEQ ID NO 774
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 774

agcgaggctt cacttggcgc 20

<210> SEQ ID NO 775
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 775

gggaagcgag gcttcacttg 20

<210> SEQ ID NO 776
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 776

gcggtcagcg atcccagggt 20

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<210> SEQ ID NO 777
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 777

gggtgccagc gcggtgatct 20

<210> SEQ ID NO 778
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 778

tgttacaaag aaagtgactg 20

<210> SEQ ID NO 779
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 779

cgatggcagc aacggaagtt 20

<210> SEQ ID NO 780
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 780

gtcagtttac gatggcagca 20

<210> SEQ ID NO 781
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 781

cagggctttg tttcgaaaaa 20

<210> SEQ ID NO 782
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 782

ccattttctt ccacagggct 20

<210> SEQ ID NO 783
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 783

atgcttcttc aagttttcca 20

<210> SEQ ID NO 784
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 784

cagaatgact ttaatgcttc 20

<210> SEQ ID NO 785
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 785

ccaccgcaaa tgcttctaga c 21

<210> SEQ ID NO 786
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 786

ccccccatt gagaagattc 20

<210> SEQ ID NO 787
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 787

ctccacctcc agcacgcgac ttct 24

<210> SEQ ID NO 788
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 788

gcggtcagcg atcccagggt 20

<210> SEQ ID NO 789
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 789

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agcagcagca gcagcagcag cagca 25

<210> SEQ ID NO 790
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 790

agcagcagca gcagcagcag 20

<210> SEQ ID NO 791
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 791

gcagcagcag cagca 15

<210> SEQ ID NO 792

<400> SEQUENCE: 792

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<210> SEQ ID NO 793
<211> LENGTH: 2611
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 793

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gccgaagtgc ggctgaggca gctccagcag ctggtgctgg acccaggctt cctgggactg 120

gagcccctgc tcgaccttct cctgggcgtc caccaggagc tgggtgcctc tcacctagcc 180

caggacaagt atgtggccga cttcttgcag tgggtggagc ccattgcagc aaggcttaag 240

gaggtccgac tgcagaggga tgattttgag attttgaagg tgatcgggcg tggggcgttc 300

agcgaggtag cggtggtgaa gatgaaacag acgggccaag tgtatgccat gaagattatg 360

aataagtggg acatgctgaa gagaggcgag gtgtcgtgct tccgggaaga aagggatgta 420

ttagtgaaag gggaccggcg ctggatcaca cagctgcact ttgccttcca ggatgagaac 480

tacctgtacc tggtcatgga atactacgtg ggcggggacc tgctaacgct gctgagcaag 540

tttggggagc ggatccccgc cgagatggct cgcttctacc tggccgagat tgtcatggcc 600

atagactccg tgcaccggct gggctacgtg cacagggaca tcaaaccaga taacattctg 660

ctggaccgat gtgggcacat tcgcctggca gacttcggct cctgcctcaa actgcagcct 720

gatggaatgg tgaggtcgct ggtggctgtg ggcaccccgg actacctgtc tcctgagatt 780

ctgcaggccg ttggtggagg gcctggggca ggcagctacg ggccagagtg tgactggtgg 840

gcactgggcg tgttcaccta tgagatgttc tatgggcaga ccccttcta cgcggactcc 900

acagccgaga catatgccaa gattgtgcac tacagggaac acttgtcgct gccgctggca 960

gacacagttg tccccgagga agctcaggac ctcattcgtg ggctgctgtg tcctgctgag 1020

ataaggctag gtcgaggtgg ggcagacttc gagggtgcca cggacacatg caatttcgat 1080

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gtggtggagg accggctcac tgccatggtg agcgggggcg gggagacgct gtcagacatg 1140

caggaagaca tgccccttgg ggtgcgcctg cccttcgtgg gctactccta ctgctgcatg 1200

gccttcagag acaatcaggt cccggacccc acccctatgg aactagaggc cctgcagttg 1260

cctgtgtcag acttgcaagg gcttgacttg cagcccccag tgtccccacc ggatcaagtg 1320

gctgaagagg ctgacctagt ggctgtccct gcccctgtgg ctgaggcaga gaccacggta 1380

acgctgcagc agctccagga agccctggaa gaagaggttc tcacccggca gagcctgagc 1440

cgcgagctgg aggccatccg gaccgccaac cagaacttct ccagccaact acaggaggcc 1500

gaggtccgaa accgagacct ggaggcgcat gttcggcagc tacaggaacg gatggagatg 1560

ctgcaggccc caggagccgc agccatcacg ggggtcccca gtccccgggc cacggatcca 1620

ccttcccatc tagatggccc cccggccgtg gctgtgggcc agtgcccgct ggtggggcca 1680

ggccccatgc accgccgtca cctgctgctc cctgccagga tccctaggcc tggcctatcc 1740

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ttcgcccccc gaaccctaag actccaagcc atctttcatt taggcctcct aggaaggtcg 1920

agcgaccagg gagcgaccca aagcgtctct gtgcccatcg ccccccccccc ccccccacc 1980

gctccgctcc acacttctgt gagcctgggt ccccacccag ctccgctcct gtgatccagg 2040

cctgccacct ggcggccggg gagggaggaa cagggctcgt gcccagcacc cctggttcct 2100

gcagagctgg tagccaccgc tgctgcagca gctgggcatt cgccgacctt gctttactca 2160

gccccgacgt ggatgggcaa actgctcagc tcatccgatt tcacttttttc actctcccag 2220

ccatcagtta caagccataa gcatgagccc cctatttcca gggacatccc attcccatag 2280

tgatggatca gcaagacctc tgccagcaca cacggagtct ttggcttcgg acagcctcac 2340

tcctgggggt tgctgcaact ccttccccgt gtacacgtct gcactctaac aacggagcca 2400

cagctgcact ccccctccc ccaaagcagt gtgggtattt attgatcttg ttatctgact 2460

cactgacaga ctccgggacc cacgttttag atgcattgag actcgacatt cctcggtatt 2520

tattgtctgt ccccacctac gacctccact cccgaccctt gcgaataaaa tacttctggt 2580

ctgccctaaa aaaaaaaaaa aaaaaaaaaa a 2611

<210> SEQ ID NO 794
<211> LENGTH: 988
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 531, 942
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 794

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cctggcttct catctgcttt tgtggtccta gctcaagacc tctaattcct ctgctgactt 120

aaatgccctt ccccagaggt cttctcaggc ctagtggaca agcttggagc cttatctgct 180

cctgcccaac attgagccaa agctccagct taccccagct tccttacaat ggaccccatt 240

gcagcaaggc ttaaggaggt ccgactgcag agggatgatt ttgagatttt gaaggtgatc 300

gggcgtgggg cgttcagcga ggtagcggtg gtgaagatga aacagacggg ccaagtgtat 360

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gccatgaaga ttatgaataa gtgggacatg ctgaagagag gcgaggtgtc gtgcttccgg 420

gaagaaaggg atgtattagt gaaaggggac cggcgctgga tcacacagct gcactttgcc 480

ttccaggatg agaactacct gtacctggtc atggaatact acgtgggcgg ngacctgcta 540

acgctgctga gcaagttttg gggagcggat ccccgccgag atggctcgct tctacctggc 600

cgagattgtc atggccatag actccgtgca ccggctgggc tacgtgcaca gggacatcaa 660

accagataac attctgctgg accgatgtgg gcacattcgc ctggcagact tcggctcctg 720

gcctcaactg cagcctgatg gaatggtgga gtcccctggt ggctgtgggc acccccggac 780

tacctgtctc ctgaaattct gcagggcctt ggtgggaggc cctggggaag gcaactacgg 840

gccaaaagtt ggaaggggggg ggcctggggg gggttcccct atgaaaagtt ctatggggag 900

gacccccttt aagcggaatc ccaggccgaa aaatatgccc angattgggc cctaacaggg 960

aaaacttttc ccctgcccct gggacaat 988

<210> SEQ ID NO 795
<211> LENGTH: 649
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 795

ggcgtgttcg cctatgagat gttctatggg cagacccccct tctacgcgga ctccacagcc 60

gagacatatg ccaagattgt gcactacagg gaacacttgt cgctgccgct ggcagacaca 120

gttgtccccg aggaagctca ggacctcatt cgtgggctgc tgtgtcctgc tgagataagg 180

ctaggtcgag gtggggcagg tgatttccag aaacatcctt tcttctttgg ccttgattgg 240

gagggtctcc gagacagtgt acccccctttt acaccagact tcgagggtgc cacggacaca 300

tgcaatttcg atgtggtgga ggaccggctc actgccatgg agacgctgtc agacatgcag 360

gaagacatgc cccttggggt gcgcctgccc ttcgtgggct actcctactg ctgcatggcc 420

ttcagagaca atcaggtccc ggaccccacc cctatggaac tagaggccct gcagttgcct 480

gtgtcagact tgcaagggct tgacttgcag cccccagtgt ccccaccgga tcaagtggtc 540

ccaactctga tccccaccga caggctgaag aggctgacct agtggctgtc cctgcccctg 600

tggctgaggc agagccacgg taacgctgca gcagctccag gaagccctg 649

<210> SEQ ID NO 796
<211> LENGTH: 527
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 796

atttcgatgt ggtggaggac cggctcactg ccatggtgag cgggggcggg gagacgctgt 60

cagacatgca ggaagacatg ccccttgggg tgcgcctgcc cttcgtgggc tactcctact 120

gctgcatggc cttcagagac aatcaggtcc cggaccccac ccctatggaa ctagaggccc 180

tgcagttgcc tgtgtcagac ttgcaagggc ttgacttgca gcccccagtg tccccaccgg 240

atcaagtggc tgaagaggct gacctagtgg ctgtccctgc ccctgtggct gaggcagaga 300

ccacggtaac gctgcagcag ctccaggaag ccctggaaga agaggttctc acccggcaga 360

gcctgagccg cgagctggag gccatccgga ccgccaacca gaacttctcc aggaggccga 420

ggtccgaaac cgagacctgg aggcgcatgt tcggcagcta caggaacgga tggagatgct 480

gcaggcccca ggaaccgcag ccatcacggg ggtccccagt cccccgg 527

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<210> SEQ ID NO 797
<211> LENGTH: 567
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 797

atggtgaggt cgctggtggc tgtgggcacc ccggactacc tgtctcctga gattctgcag 60

gccgttggtg gagggcctgg ggcaggcagc tacgggccag agtgtgactg gtgggcactg 120

ggcgtgttcg cctatgagat gttctatggg cagacccccc tctacgcgga ctccacagcc 180

gagacatatg ccaagattgt gcactacagg gaacacttgt cgctgccgct ggcagacaca 240

gttgtccccg aggaagctca ggacctcatt cgtgggctgc tgtgtcctgc tgagataagg 300

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gagggtctcc gagacagtgt acccccctttt acaccagact tcgagggtgc cacggacaca 420

tgcaatttcg atgtggtgga ggaccggctc actgccatgg tgagcggggg cggggtatga 480

ggacacacag gtgaccagtc cccaagacag tgagtgaggc ttcactcttg gcagtactaa 540

aattgaatgt agggggctgg gctcttg 567

<210> SEQ ID NO 798
<211> LENGTH: 2474
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 798

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tgccttccag gatgagaact acctgtacct ggtcatggaa tactacgtgg gcggggacct 120

gctaacgctg ctgagcaagt ttggggagcg gatccccgcc gagatggctc gcttctacct 180

ggccgagatt gtcatggcca tagactccgt gcaccggctg ggctacgtgc acagggacat 240

caaaccagat aacattctgc tggaccgatg tgggcacatt cgcctggcag acttcggctc 300

ctgcctcaaa ctgcagcctg atggaatggt gaggtcgctg gtggctgtgg gcaccccgga 360

ctacctgtct cctgagattc tgcaggccgt tggtggaggg cctggggcag gcagctacgg 420

gccagagtgt gactggtggg cactgggcgt gttcgcctat gagatgttct atgggcagac 480

ccccttctac gcggactcca cagccgagac atatgccaag attgtgcact acagggaaca 540

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gctgctgtgt cctgctgaga taaggctagg tcgagacttc gagggtgcca cggacacatg 660

caatttcgat gtggtggagg accggctcac tgccatggtg agcgggggcg gggagacgct 720

gtcagacatg caggaagaca tgccccttgg ggtgcgcctg cccttcgtgg gctactccta 780

ctgctgcatg gccttcagag acaatcaggt cccggacccc acccctatgg aactagaggc 840

cctgcagttg cctgtgtcag acttgcaagg gcttgacttg cagcccccag tgtccccacc 900

ggatcaagtg gctgaagagg ccgacctagt ggctgtccct gcccctgtgg ctgaggcaga 960

gaccacggta acgctgcagc agctccagga agccctggaa gaagaggttc tcacccggca 1020

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ggggcactgg gtggagatgg ggggcatgtt gggtgtgtga accctcgggg caggggagga 1260

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tccaggcctg ccacctggcg gccggggagg gaggaacagg gctcgtgccc agcacccctg 1980

gttcctgcag agctggtagc caccgctgct gcagcagctg ggcattcgcc gaccttgctt 2040

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tcccagccat cagttacaag ccataagcat gagcccccta tttccaggga catcccattc 2160

ccatagtgat ggatcagcaa gacctctgcc agcacacacg gagtctttgg cttcggacag 2220

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ctgactcact gacagactcc gggacccacg ttttagatgc attgagactc gacattcctc 2400

ggtatttatt gtctgtcccc acctacgacc tccactcccg acccttgcga ataaaatact 2460

tctggtctgc ccta 2474

<210> SEQ ID NO 799
<211> LENGTH: 2135
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 799

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tgccttccag gatgagaact acctgtacct ggtcatggaa tactacgtgg gcggggacct 120

gctaacgctg ctgagcaagt ttggggagcg gatccccgcc gagatggctc gcttctacct 180

ggccgagatt gtcatggcca tagactccgt gcaccggctg ggctacgtgc acagggacat 240

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

<400> SEQUENCE: 806

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gcttgcacgt gtggct 16

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ggttgtgaac tggcag 16

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gagcggttgt gaactg 16

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

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ctgccttccc aggc 14

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gcactttgcg aaccaa 16

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<400> SEQUENCE: 825

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<210> SEQ ID NO 828
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<210> SEQ ID NO 829
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<400> SEQUENCE: 830

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<210> SEQ ID NO 831
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<400> SEQUENCE: 831

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<210> SEQ ID NO 832
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<400> SEQUENCE: 832

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<400> SEQUENCE: 834

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<210> SEQ ID NO 836
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 836

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<210> SEQ ID NO 837
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 837

aatgacttta atgc 14

1.-**124**. (canceled)

125. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of nucleobases 2159-2182 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is complementary to SEQ ID NO: 1.

126. The compound of claim **125**, wherein the modified oligonucleotide is a single-stranded oligonucleotide.

127. The compound of claim **125**, wherein the nucleobase sequence of the modified oligonucleotide is 80% complementary to SEQ ID NO: 1.

128. The compound of claim **125**, wherein the nucleobase sequence of the modified oligonucleotide is 90% complementary to SEQ ID NO: 1.

129. The compound of claim **125**, wherein the nucleobase sequence of the modified oligonucleotide is 95% complementary to SEQ ID NO: 1.

130. The compound of claim **125**, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to SEQ ID NO: 1.

131. The compound of claim **125**, wherein at least one nucleoside comprises a modified sugar.

132. The compound of claim **131**, wherein at least one modified sugar is a bicyclic sugar.

133. The compound of claim **131**, wherein at least one modified sugar comprises a 2'-O-methoxyethyl.

134. The compound of claim **125**, wherein at least one nucleoside comprises a modified nucleobase.

135. The compound of claim **134**, wherein the modified nucleobase is a 5-methylcytosine.

136. The compound of claim **125**, wherein at least one internucleoside linkage is a modified internucleoside linkage.

137. The compound of claim **136**, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

138. The compound of claim **125**, wherein the modified 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 between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

139. The compound of claim **125**, wherein the modified oligonucleotide consists of 20 linked nucleosides and 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 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.

140. The compound of claim **139**, wherein the modified oligonucleotide has a nucleobase sequence that consists of the nucleobase sequence of SEQ ID NO. 109.

141. A pharmaceutical composition comprising the compound of claim **140** and a pharmaceutically acceptable carrier or diluent.

142. A method of reducing DMPK expression in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to DMPK, wherein expression of DMPK is reduced in the animal.

143. A method of preferentially reducing CUGexp DMPK RNA, reducing myotonia or reducing spliceopathyin an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to DMPK, wherein the modified oligonucleotide reduces DMPK expression in the animal, thereby preferentially reducing CUGexp DMPK RNA, reducing myotonia or reducing spliceopathy in the animal.

* * * * *