**Abstract**

The invention relates to a double-stranded ribonucleic acid (dsRNA) for inhibiting the expression of the Nav1.8 gene (Nav1.8 gene), comprising an antisense strand having a nucleotide sequence which is less than 25 nucleotides in length and which is substantially complementary to at least a part of the Nav1.8 gene. The invention also relates to a pharmaceutical composition comprising the dsRNA together with a pharmaceutically acceptable carrier; methods for treating diseases caused by the expression of the Nav1.8 gene using the pharmaceutical composition; and methods for inhibiting the expression of the Nav1.8 gene in a cell.
FIG. 4
FIG. 6

Paw Withdrawal Threshold (g ± SEM)

Baseline

Day 4
N=5

PBS
AL-DP-4461
AL-DP-4459
AL-DP-6980

PBS
AL-DP-4461 (0.5mg/bolus)
AL-DP-4459 (0.15mg/bolus)
AL-DP-6980 (0.15mg/bolus)

bolus BID
FIG. 7
Days Post-SNL N=6-8

A: AL-DP-4459 (0.16mg/d)
B: PBS
C: AL-DP-4459 (0.15mg)

FIG. 9
FIG. 10

Bar charts showing the percentage of strands remaining over time for different samples. The x-axis represents time points in hours (0, 1, 2, 4, 8, 24, 48). The y-axis represents the percentage of strands remaining. The bars are color-coded to indicate antisense and sense strands.

Samples include:
- AL-DP-6209
- AL-DP-6050
- AL-DP-6217
- AL-DP-6219

Each bar chart compares the percentage of strands remaining for the antisense and sense strands across different time points.
FIG. 11

AL-DP-4459

% strand remaining

Timepoint [h]

antisense

sense

PBS-48
FIG. 12

Nav1.8/SNCA, % relative to L2000 only

- AL-DP-6050
- AL-DP-4459
- L2000

siRNA, nM

0.1 1 10 100 1000
FIG. 13

* p < 0.05 vs PBS
^ p < 0.05 vs d3

K: AL-DP-6050 (0.15 mg BID)
L: PBS

Paw Withdrawal Latency (sec ± SEM)

Days Following SNL Surgery

0 5 10 15 20 25
BL 2 4 6 8
FIG. 14

- A = PBS IT bolus
- B = 5 ug AL-DP-6050 IT bolus
- C = 0.5 mg AL-DP-6050 IV bolus
- D = 0.24 mg/d AL-DP-6050 IV pump

Paw Withdrawal Latency (sec ± SEM)

Days Following SNL Surgery
COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF NAV1.8 GENE

RELATED APPLICATIONS

[0001] This application is a divisional of U.S. patent application Ser. No. 12/487,605, filed Jun. 18, 2009, which is a divisional of U.S. patent application Ser. No. 11/593,099, filed Nov. 3, 2006, which claims the benefit of U.S. Provisional Application No. 60/733,816, filed Nov. 4, 2005; U.S. Provisional Application No. 60/741,586, filed Dec. 2, 2005; U.S. Provisional Application No. 60/763,202, filed Jan. 26, 2006; U.S. Provisional Application No. 60/795,443, filed Apr. 27, 2006; and U.S. Provisional Application No. 60/849,364, filed Oct. 4, 2006. The contents of these prior applications are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jun. 17, 2009, is named 18217_US_sequencelisting.txt, is 225 kilobytes in size, and consists of 609 sequences.

FIELD OF THE INVENTION

[0003] This invention relates to double-stranded ribonucleic acid (dsRNA), and its use in mediating RNA interference to inhibit the expression of the Nav1.8 gene and the use of the dsRNA to treat pain.

BACKGROUND OF THE INVENTION

[0004] Neuropathic pain can be classified as peripheral and central neuropathic pain. Peripheral neuropathic pain is caused by injury or infection of peripheral sensory nerves, whereas central neuropathic pain is caused by damage to the CNS and/or the spinal cord. Both peripheral and central neuropathic pain can occur without obvious initial nerve damage.

[0005] A similar definition is given by the International Association for the Study of Pain (IASP, Seattle, Wash., USA): peripheral neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system. Central neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the central nervous system.

[0006] Peripheral lesions may be lesions of peripheral nerves, e.g., diabetic neuropathy, drug-induced neuropathy, e.g., upon chemotherapy, lesions of nerve roots and posterior ganglia, e.g., post-herpetic neuralgia or nerve root avulsions, neuropathic cancer pain due to compression of peripheral nerves, nerve plexuses and nerve roots, etc. Central lesions may be lesions due to infarction, compressive tumors or abscesses, e.g. in the brainstem, or may be spinal cord lesions due to injury or operations (Jain K K, Emerging Drugs, 2000, 5:241-257; McQuay, 2002, European Journal of Pain 6 (Suppl. A): 11-18).

[0007] The above examples of peripheral and central neuropathic pain demonstrate that peripheral and central neuropathic pain are distinguished not only by the anatomical location of the lesion or dysfunction, but they also demonstrate that peripheral and central neuropathic pain can be distinguished by its mechanisms (McQuay, supra). Consequently, there is no clear relation between drug action mechanism and the effect in distinct pain conditions or for single drug classes and different pain conditions (Sindrup S H, Jensen T S, Pain 1999, 83:389-400).

[0008] Common analgesics like opioids and non-steroidal anti-inflammatory drugs (NSAIDs) improve only insufficiently chronic abnormal pain syndromes as peripheral and central neuropathic pain due to insufficient efficacy and/or dose-limiting side effects. In the search for alternative treatment regimes to produce satisfactory and sustained pain relief, corticosteroids, conduction blockade, glycerol, anti-convulsants, anti-arrhythmics, antidepressants, local anesthetics, topical agents such as capsaicin, gangliosides and electrostimulation have been tried, but only a subset of patients with neuropathic pain respond to such treatments and typically, significant pain remains even in these responders. The critical issue with current therapies is the therapeutic window; a particular treatment might have potential for efficacy but the patients are not ‘treated to effect’ because of limiting side effects upon dose escalation.

[0009] Central neuropathic pain is a form of neuropathic pain which is a particularly difficult form to be treated (Yezierski and Burchiel, 2002). Due to lesions in the spinothalamocortical pathways, ectopic neuronal discharges can occur in different neurons of the spinal cord and brain. Hyperexcitability in damaged areas of the central nervous system plays a major role in the development of central neuropathic pain. Patients with central neuropathic pain almost always have stimulus-independent pain. In addition, in the case of spinal cord injury, for example, stimulus-dependent pain may be present, usually because skin areas or viscera below the lesions are allodynic. Thus, partial spinal lesions may tend to produce pain to a greater extent than do complete lesions.

[0010] Other accepted forms of central neuropathic pain or diseases associated with central neuropathic pain exist. Examples include inflammatory CNS diseases such as multiple sclerosis, myelitis or syphilis, ischemia, hemorrhages or arteriovenous malformations (e.g. post-stroke neuropathic pain) located in the thalamus, spinothalamic pathway or thalamocortical projections, and sympathomimetics (Kolzenburg, Pain 2002—An Updated Review: Refreshers Course Syllabus; IASP Press, Seattle, 2002).


[0012] In general, voltage-gated sodium channels (Navs) are responsible for initiating the rapid upstroke of action potentials in excitable tissue in nervous system, which transmit the electrical signals that compose and encode normal and aberrant pain sensations. Antagonists of NaV channels can attenuate these pain signals and are useful for treating a vari-


[0014] Taken together, these data support a role for NaV1.8 in the detection and transmission of inflammatory and neuropathic pain.

[0015] Recently, double-stranded RNA molecules (dsRNA) have been shown to block gene expression in a highly conserved regulatory mechanism known as RNA interference (RNAI). WO 99/32619 (Fire et al.) discloses the use of a dsRNA of at least 25 nucleotides in length to inhibit the expression of the Nav1.8 gene in C. elegans. dsRNA has also been shown to degrade target RNA in other organisms, including plants (see, e.g., WO 99/53050, Waterhouse et al.; and WO 99/61631, Heifetz et al.), Drosophila (see, e.g., Yang, D., et al., Curr. Biol. (2000) 10:1191-1200) and mammals (see WO 00/44895, Limmer; and DE 101 00 586, Kretzter et al.). This natural mechanism has now become the focus for the development of a new class of pharmaceutical agents for treating disorders that are caused by the aberrant or unwanted regulation of a gene.

[0016] Despite significant advances in the field of RNAi and advances in the treatment of pain, there remains a need for an agent that can selectively and efficiently silence the Nav1.8 gene using the cell’s own RNAi machinery that has both high biological activity and in vivo stability, and that can effectively inhibit expression of a target Nav1.8 gene for use in treating pain.

SUMMARY OF THE INVENTION

[0017] The invention provides double-stranded ribonucleic acid (dsRNA), as well as compositions and methods for inhibiting the expression of the Nav1.8 gene in a cell or mammal using such dsRNA. The invention also provides compositions and methods for treating pathological conditions and diseases caused by the expression of the Nav1.8 gene, such as in the propagation of pain signals in neuropathic and inflammatory pain. The dsRNA of the invention comprises an RNA strand (the antisense strand) having a region which is less than 30 nucleotides in length and is substantially complementary to at least part of an mRNA transcript of the Nav1.8 gene.

[0018] In one embodiment, the invention provides double-stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of the Nav1.8 gene. The dsRNA comprises at least two sequences that are complementary to each other. The dsRNA comprises a sense strand comprising a first sequence and an antisense strand comprising a second sequence. The antisense strand comprises a nucleotide sequence which is substantially complementary to at least part of an mRNA encoding Nav1.8, and the region of complementarity is less than 30 nucleotides in length. The dsRNA, upon contacting with a cell expressing the Nav1.8, inhibits the expression of the Nav1.8 gene by at least 20%.

[0019] For example, the dsRNA molecules of the invention can be comprised of a first sequence of the dsRNA that is selected from the group consisting of the sense sequences of Tables 1, 4 and 6 and the second sequence is selected from the group consisting of the antisense sequences of Tables 1, 4 and 6. The dsRNA molecules of the invention can be comprised of naturally occurring nucleotides or can be comprised of at least one modified nucleotide, such as a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholestery derivative or docosahexaenoic acid bisdecyllamide group. Alterna-
tively, the modified nucleotide may be chosen from the group of: a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-aminomodified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, a phosphorimidate, and a non-natural base comprising nucleotide. Preferably, the first sequence of said dsRNA is selected from the group consisting of the sense sequences of Tables 1, 4 and 6 and the second sequence is selected from the group consisting of the anti-sense sequences of Tables 1, 4 and 6.

[0020] In another embodiment, the invention provides a cell comprising one of the dsRNAs of the invention. The cell is preferably a mammalian cell, such as a human cell.

[0021] In another embodiment, the invention provides a pharmaceutical composition for inhibiting the expression of the Nav1.8 gene in an organism, comprising one or more of the dsRNA of the invention and a pharmaceutically acceptable carrier.

[0022] In another embodiment, the invention provides a method for inhibiting the expression of the Nav1.8 gene in a cell, comprising the following steps:

[0023] (a) introducing into the cell a double-stranded ribonucleic acid (dsRNA), wherein the dsRNA comprises at least two sequences that are complementary to each other. The dsRNA comprises a sense strand comprising a first sequence and an antisense strand comprising a second sequence. The antisense strand comprises a region of complementarity which is substantially complementary to at least a part of an mRNA encoding Nav1.8, and wherein the region of complementarity is less than 30 nucleotides in length and wherein the dsRNA, upon contact with a cell expressing the Nav1.8, inhibits expression of the Nav1.8 gene by at least 20%; and

[0024] (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the Nav1.8 gene, thereby inhibiting expression of the Nav1.8 gene in the cell.

[0025] In another embodiment, the invention provides methods for treating, preventing or managing pain comprising administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of one or more of the dsRNAs of the invention.

[0026] In another embodiment, the invention provides vectors for inhibiting the expression of the Nav1.8 gene in a cell, comprising a regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of one of the dsRNA of the invention.

[0027] In another embodiment, the invention provides a cell comprising a vector for inhibiting the expression of the Nav1.8 gene in a cell. The vector comprises a regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of one of the dsRNA of the invention.

[0030] FIG. 3. In vitro activity of the dsRNAs provided in Table 1 against endogenous Nav.1.8 mRNA in primary cultures of rat dorsal root ganglion cells.


[0032] FIG. 5. In vivo efficacy of dsRNA AL-DP-6209 with iFECT against complete Freund’s adjuvant-induced tactile hyperalgesia in rats.


[0042] FIG. 15. Structure of ND98 lipid

DETAILED DESCRIPTION OF THE INVENTION

[0043] The invention provides double-stranded ribonucleic acid (dsRNA), as well as compositions and methods for inhibiting the expression of the Nav1.8 gene in a cell or mammal using the dsRNA. The invention also provides compositions and methods for treating pathological conditions and diseases in a mammal caused by the expression of the Nav1.8 gene using dsRNA. dsRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). The process occurs in a wide variety of organisms, including mammals and other vertebrates.

[0044] The dsRNA of the invention comprises an RNA strand (the antisense strand) having a region which is less than 30 nucleotides in length and which is substantially complementary to at least part of an mRNA transcript of the Nav1.8 gene. The use of these dsRNAs enables the targeted degradation of mRNAs of genes that are implicated in pain response in mammals. Using cell-based and animal assays, the present inventors have demonstrated that very low dosages of these dsRNA can specifically and efficiently mediate RNAi, resulting in significant inhibition of expression of the Nav1.8 gene. Thus, the methods and compositions of the invention comprising these dsRNAs are useful for treating pain.

[0045] The following detailed description discloses how to make and use the dsRNA and compositions containing
dsRNA to inhibit the expression of a target Nav1.8 gene, as well as compositions and methods for treating diseases and disorders caused by the expression of Nav1.8, such as neuropathic and inflammatory pain. The pharmaceutical compositions of the invention comprise a dsRNA having an antisense strand comprising a region of complementarity which is less than 30 nucleotides in length and is substantially complementary to at least part of an RNA transcript of the Nav1.8 gene, together with a pharmaceutically acceptable carrier.

Accordingly, certain aspects of the invention provide pharmaceutical compositions comprising the dsRNA of the invention together with a pharmaceutically acceptable carrier, methods of using the compositions to inhibit expression of the Nav1.8 gene, and methods of using the pharmaceutical compositions to treat diseases caused by expression of the Nav1.8 gene.

I. DEFINITIONS

[0047] For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in other parts of this specification and its definition provided in this section, the definition in this section shall prevail.

[0048] “G,” “C,” “A” and “U” each generally stand for a nucleotide that contains guanine, cytosine, adenine, and uracil as a base, respectively. However, it will be understood that the term “ribonucleotide” or “nucleotide” can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person is well aware that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of the invention by a nucleotide containing, for example, inosine. Sequences comprising such replacement moieties are embodiments of the invention.

[0049] By “Nav1.8” as used herein is meant, any Nav1.8 protein, polypeptide, or polypeptide associated with the development or maintenance of an ion channel. The terms “Nav1.8” also refer to nucleic acid sequences encoding any Nav1.8 protein, polypeptide, or polypeptide. For the Examples, the Nav1.8 mRNA sequences used were human (NM_006514), mouse (NM_009134), rat (NM_017247) and dog (NM001003203) mRNA sequences.

[0050] As used herein, “target sequence” refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of the Nav1.8 gene, including mRNA that is a product of RNA processing of a primary transcription product.

[0051] As used herein, the term “strand comprising a sequence” refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

[0052] As used herein, and unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions may include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50° C. or 70° C. for 12-16 hours followed by washing. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

[0053] This includes base-pairing of the oligonucleotide or polynucleotide comprising the first nucleotide sequence to the oligonucleotide or polynucleotide comprising the second nucleotide sequence over the entire length of the first and second nucleotide sequence. Such sequences can be referred to as “fully complementary” with respect to each other herein. However, where a first sequence is referred to as “substantially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but preferably not more than 4, 3 or 2 mismatched base pairs upon hybridization, while retaining the ability to hybridize under the conditions most relevant to their ultimate application. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to as “fully complementary” for the purposes of the invention.

[0054] “Complementary” sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled.

[0055] The terms “complementary”, “fully complementary” and “substantially complementary” herein may be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of a dsRNA and a target sequence, as will be understood from the context of their use.

[0056] As used herein, a polynucleotide which is “substantially complementary to at least part of a messenger RNA (mRNA) refers to a polynucleotide which is substantially complementary to a contiguous portion of the mRNA of interest (e.g., encoding Nav1.8). For example, a polynucleotide is complementary to at least a part of a Nav1.8 mRNA if the sequence is substantially complementary to a noninterrupted portion of an mRNA encoding Nav1.8.

[0057] The term “double-stranded RNA” or “dsRNA”, as used herein, refers to a polynucleotide acid molecule, or complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary, as defined above, nucleic acid strands. The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3’-end of one strand and the 5’-end of the respective other strand forming the duplex structure, the con-
necting RNA chain is referred to as a “hairpin loop”. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a “linker”. The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA. In addition to the duplex structure, a dsRNA may comprise one or more nucleotide overhangs.

[0058] As used herein, a “nucleotide overhang” refers to the unpaired nucleotide or nucleotides that protrude from the duplex structure of a dsRNA when a 3'-end of one strand of the dsRNA extends beyond the 5'-end of the other strand, or vice versa. “Blunt” or “blunt end” means that there are no unpaired nucleotides at that end of the dsRNA, i.e., no nucleotide overhang. A “blunt ended” dsRNA is a dsRNA that is double-stranded over its entire length, i.e., no nucleotide overhang at either end of the molecule.

[0059] The term “antisense strand” refers to the strand of a dsRNA which includes a region that is substantially complementary to a target sequence. As used herein, the term “region of complementarity” refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches are most tolerated in the terminal regions and, if present, are preferably in a terminal region or regions, e.g., within 6, 5, 4, 3, or 2 nucleotides of the 5’ and/or 3’ terminus.

[0060] The term “sense strand,” as used herein, refers to the strand of a dsRNA that includes a region that is substantially complementary to a region of the antisense strand.

[0061] “Introducing into a cell”, when referring to a dsRNA, means facilitating uptake or absorption into the cell, as is understood by those skilled in the art. Absorption or uptake of dsRNA can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. The meaning of this term is not limited to cells in vitro; a dsRNA may also be “introduced into a cell”; wherein the cell is part of a living organism. In such instance, introduction into the cell will include the delivery to the organism. For example, for in vivo delivery, dsRNA can be injected into a tissue site or administered systemically. In vitro introduction into a cell includes methods known in the art such as electroporation and lipofection.

[0062] The terms “silence” and “inhibit the expression of”, in as far as they refer to the Nav1.8 gene, herein refer to the at least partial suppression of the expression of the Nav1.8 gene, as manifested by a reduction of the amount of mRNA transcribed from the Nav1.8 gene which may be isolated from a first cell or group of cells in which the Nav1.8 gene is transcribed and which has or have been treated such that the expression of the Nav1.8 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells). The degree of inhibition is usually expressed in terms of

\[
\frac{(mRNA \text{ in control cells}) - (mRNA \text{ in treated cells})}{(mRNA \text{ in control cells})} \times 100\%
\]

[0063] Alternatively, the degree of inhibition may be given in terms of a reduction of a parameter that is functionally linked to Nav1.8 gene transcription, e.g. the amount of protein encoded by the Nav1.8 gene which is secreted by a cell, or the number of cells displaying a certain phenotype, e.g. apoptosis. In principle, Nav1.8 gene silencing may be determined in any cell expressing the target, either constitutively or by genomic engineering, and by any appropriate assay. However, when a reference is needed in order to determine whether a given siRNA inhibits the expression of the Nav1.8 gene by a certain degree and therefore is encompassed by the instant invention, the assay provided in the Examples below shall serve as such reference.

[0064] For example, in certain instances, expression of the Nav1.8 gene is suppressed by at least about 20%, 25%, 35%, or 50% by administration of the double-stranded oligonucleotide of the invention. In a preferred embodiment, the Nav1.8 gene is suppressed by at least about 60%, 70%, or 80% by administration of the double-stranded oligonucleotide of the invention. In a more preferred embodiment, the Nav1.8 gene is suppressed by at least about 85%, 90%, or 95% by administration of the double-stranded oligonucleotide of the invention. In a most preferred embodiment, the Nav1.8 gene is suppressed by at least about 98%, 99% or more by administration of the double-stranded oligonucleotide of the invention.

[0065] The terms “treat”, “treatment”, and the like, refer to relief from or alleviation of the perception of pain, including the relief from or alleviation of the intensity and/or duration of a pain (e.g., burning sensation, tingling, electric-shock-like feelings, etc.) experienced by a subject in response to a given stimulus (e.g., pressure, tissue injury, cold temperature, etc.). Relief from or alleviation of the perception of pain can be any detectable decrease in the intensity or duration of pain. Treatment can occur in a subject (e.g., a human or companion animal) suffering from a pain condition or having one or more symptoms of a pain-related disorder that can be treated according to the present invention, or in an animal model of pain, such as the SNI rat model of neuropathic pain or CFA rat model of chronic pain described herein, or another animal model of pain. In the context of the present invention insofar as it relates to any of the other conditions recited herein below (other than pain), the terms “treat”, “treatment”, and the like mean to relieve or alleviate at least one symptom associated with such condition, or to slow or reverse the progression of such condition.

[0066] As used herein, the phrases “therapeutically effective amount” and “prophylactically effective amount” refer to an amount that provides a therapeutic benefit in the treatment, prevention, or management of pain or an overt symptom of pain. The specific amount that is therapeutically effective can be readily determined by ordinary medical practitioner, and may vary depending on factors known in the art, such as, e.g. the type of pain, the patient's history and age, the stage of pain, and the administration of other anti-pain agents.

[0067] As used herein, a “pharmaceutical composition” comprises a pharmaceutically effective amount of a dsRNA and a pharmaceutically acceptable carrier. As used herein, “pharmaceutically effective amount”, “therapeutically effective amount” or simply “effective amount” refers to that amount of an RNA effective to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 25% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount
of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 25% reduction in that parameter.

The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

As used herein, a “transformed cell” is a cell into which a vector has been introduced from which a dsRNA molecule may be expressed.

II. Double-Stranded Ribonucleic Acid (dsRNA)

In one embodiment, the invention provides double-stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of the Nav1.8 gene in a cell or mammal, wherein the dsRNA comprises an antisense strand comprising a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of the Nav1.8 gene, and wherein the region of complementarity is less than 30 nucleotides in length and wherein said dsRNA, upon contact with a cell expressing said Nav1.8 gene, inhibits the expression of said Nav1.8 gene by at least 20%. The dsRNA comprises two RNA strands that are sufficiently complementary to hybridize to form a duplex structure. One strand of the dsRNA (the antisense strand) comprises a region of complementarity that is substantially complementary, and preferably fully complementary, to a target sequence, derived from the sequence of an mRNA formed during the expression of the Nav1.8 gene, the other strand (the sense strand) comprises a region which is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. Preferably, the duplex structure is between 15 and 30, more preferably between 18 and 25, yet more preferably between 19 and 24, and most preferably between 21 and 23 base pairs in length. Similarly, the region of complementarity to the target sequence is between 15 and 30, more preferably between 18 and 25, yet more preferably between 19 and 24, and most preferably between 21 and 23 nucleotides in length. The dsRNA of the invention may further comprise one or more single-stranded nucleotide overhang(s). The dsRNA can be synthesized by standard methods known in the art as further discussed below, e.g., by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc. In a preferred embodiment, the Nav1.8 gene is the human Nav1.8 gene. In specific embodiments, the antisense strand of the dsRNA comprises the antisense sequences of Tables 1, 4 and 6 and the second sequence is selected from the group consisting of the sense sequences of Tables 1, 4 and 6.

In further embodiments, the dsRNA comprises at least one nucleotide sequence selected from the groups of sequences provided in Tables 1, 4 and 6. In other embodiments, the dsRNA comprises at least two sequences selected from this group, wherein one of the at least two sequences is complementary to another of the at least two sequences, and one of the at least two sequences is substantially complementary to a sequence of an mRNA generated in the expression of the Nav1.8 gene. Preferably, the dsRNA comprises two oligonucleotides, wherein one oligonucleotide is described by Tables 1, 4 and 6 and the second oligonucleotide is described by Tables 1, 4 and 6.

The skilled person is well aware that dsRNAs comprising a duplex structure of between 20 and 23, but specifically 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashar et al., EMBO 2001, 20:6877-6888). However, others have found that shorter or longer dsRNAs can be effective as well. In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in Tables 1, 4 and 6, the dsRNAs of the invention can comprise at least one strand of a length of minimally 21 nt. It can be reasonably expected that shorter dsRNAs comprising one of the sequences of Tables 1, 4 and 6 minus only a few nucleotides on one or both ends may be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs comprising a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one of the sequences of Tables 1, 4 and 6, and differing in their ability to inhibit the expression of the Nav1.8 gene in a FACS assay as described herein below by not more than 5, 10, 15, 20, 25, or 30% inhibition from a dsRNA comprising the full sequence, are contemplated by the invention.

The dsRNA of the invention can contain one or more mismatches to the target sequence.

In a preferred embodiment, the dsRNA of the invention contains no more than 3 mismatches. If the antisense strand of the dsRNA contains mismatches to a target sequence, it is preferable that the area of mismatch not be located in the center of the region of complementarity. If the antisense strand of the dsRNA contains mismatches to the target sequence, it is preferable that the mismatch be restricted to 5 nucleotides from either end, for example 5, 4, 3, 2, or 1 nucleotide from either the 5' or 3' end of the region of complementarity. For example, for a 23 nucleotide dsRNA strand which is complementary to a region of the Nav1.8 gene, the dsRNA preferably does not contain any mismatch within the central 13 nucleotides. The methods described within the invention can be used to determine whether a dsRNA containing a mismatch to a target sequence is effective in inhibiting the expression of the Nav1.8 gene. Consideration of the efficacy of dsRNAs with mismatches in inhibiting expression of the Nav1.8 gene is important, especially if the particular region of complementarity in the Nav1.8 gene is known to have polymorphic sequence variation within the population.

In one embodiment, at least one end of the dsRNA has a single-stranded nucleotide overhang of 1 to 4, preferably 1 or 2 nucleotides. dsRNAs having at least one nucleotide overhang have unexpectedly superior inhibitory properties than their blunt-ended counterparts. Moreover, the present inventors have discovered that the presence of only one nucleotide overhang strengthens the interference activity of the dsRNA, without affecting its overall stability. dsRNA having only one overhang has proven particularly stable and
effective in vivo, as well as in a variety of cells, cell culture mediums, blood, and serum. Preferably, the single-stranded overhang is located at the 3'-terminal end of the antisense strand or, alternatively, at the 3'-terminal end of the sense strand. The dsRNA may also have a blunt end, preferably located at the 5'-end of the antisense strand. Such dsRNAs have improved stability and inhibitory activity, thus allowing administration at low dosages, i.e., less than 5 mg/kg body weight of the recipient per day. Preferably, the antisense strand of the dsRNA has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

[0076] In yet another embodiment, the dsRNA is chemically modified to enhance stability. The nucleic acids of the invention may be synthesized and/or modified by methods well established in the art, such as those described in “Current protocols in nucleic acid chemistry”, Beaucage, S., l. al., (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, which is hereby incorporated herein by reference. Chemical modifications may include, but are not limited to 2' modifications, introduction of non-natural bases, covalent attachment to a ligand, and replacement of phosphate linkages with thiophosphorane linkages. In this embodiment, the integrity of the duplex structure is strengthened by at least one, and preferably two, chemical linkages. Chemical linking may be achieved by any of a variety of well-known techniques, for example by introducing covalent, ionic or hydrogen bonds; hydrophobic interactions, van der Waals or stacking interactions; by means of metal-ion coordination, or through use of purine analogues. Preferably, the chemical groups that can be used to modify the dsRNA include, without limitation, methylene blue; bifunctional groups, preferably bis-(2-chloroethyl)amine; N-acetyl-N'-(p-glycyl) benzoyl cysteamine; 4-thiouracil; and psoralen. In one preferred embodiment, the linker is a hexa-ethylene glycol linker. In this case, the dsRNA are produced by solid phase synthesis and the hexa-ethylene glycol linker is incorporated according to standard methods (e.g., Williams, D. J., and K. B. Hall, *Biochem.*, (1996) 35:14665-14670). In a particular embodiment, the 3'-end of the antisense strand and the 3'-end of the sense strand are chemically linked via a hexaethylene glycol linker. In another embodiment, the 3'-end of the sense strand and the 3'-end of the antisense strand are phosphorothioate or phosphorodithioate groups. The chemical bond at the ends of the dsRNA is preferably formed by triple-helix bonds. Table 1 provides examples of modified RNA agents of the invention.

[0077] In certain embodiments, a chemical bond may be formed by means of one or several bonding groups, wherein such bonding groups are preferably poly-(oxyphosphino-cooxy-1,3-propandiol) and/or polyethylene glycol chains. In other embodiments, a chemical bond may also be formed by means of purine analogs introduced into the double-stranded structure instead of purines. In further embodiments, a chemical bond may be formed by azabenzenes units introduced into the double-stranded structure. In still further embodiments, a chemical bond may be formed by branched nucleotide analogs instead of nucleotides introduced into the double-stranded structure. In certain embodiments, a chemical bond may be induced by ultraviolet light.

[0078] In yet another embodiment, the nucleotides at one or both of the two single strands may be modified to prevent or inhibit the activation of cellular enzymes, such as, for example, without limitation, certain nuclease. Techniques for inhibiting the activation of cellular enzymes are known in the art including, but not limited to, 2'-amino modifications, 2'-fluoro modifications, 2'-alkyl modifications, uncharged backbone modifications, morpholino modifications, 2'-O-methyl modifications, and phosphoramidate (see, e.g., Wagner, *Nat. Med.* (1995) 1:1116-8). Thus, at least one 2'-hydroxyl group of the nucleotides on a dsRNA is replaced by a chemical group, preferably by a 2'-fluoro or a 2'-O-methyl group. Also, at least one nucleotide may be modified to form a locked nucleotide. Such locked nucleotides can be formed by methylene or ethylene bridge that connects the 2'-oxygen of ribose with the 4'-carbon of ribose. Oligonucleotides containing the locked nucleotide are described in Koshkin, A. A., et al., *Tetrahedron* (1998), 54: 3607-3630 and Obika, S. et al., *Tetrahedron Lett.* (1998), 39: 5401-5404. Introduction of a locked nucleotide into an oligonucleotide improves the affinity for complementary sequences and increases the melting temperature by several degrees (Braunsch, D. A. and D. R. Corey, *Chem. Biol.* (2001), 8:1-7).

[0079] Conjugating a ligand to a dsRNA can enhance its cellular absorption. In certain instances, a hydrophobic ligand is conjugated to the dsRNA to facilitate direct permeation of the cellular membrane. Alternatively, the ligand conjugated to the dsRNA is a substrate for receptor-mediated endocytosis. These approaches have been used to facilitate cell permeation of antisense oligonucleotides. For example, cholesterol has been conjugated to various antisense oligonucleotides resulting in compounds that are substantially more active compared to their non-conjugated analogs. See M. Manoharan *Antisense & Nucleic Acid Drug Development* 2002, 12, 103. Other lipophilic compounds that have been conjugated to oligonucleotides include 1-pyrene butyric acid, 1,3-bis-O-(hexadecyl)glycerol, and menthol. One example of a ligand for receptor-mediated endocytosis is folic acid. Folic acid enters the cell by folate-receptor-mediated endocytosis. dsRNA compounds bearing folic acid would be efficiently transported into the cell via the folate-receptor-mediated endocytosis. Li and coworkers report that attachment of folic acid to the 3'-terminus of an oligonucleotide resulted in an 8-fold increase in cellular uptake of the oligonucleotide. Li, S.; Deshukh, H. M.; Huang, L. *Pharm. Res.* 1998, 15, 1540. Other ligands that have been conjugated to oligonucleotides include polyethylene glycol, polyethylene glycol-grafted to oligonucleotides, cross-linking agents, porphyrin conjugates, and delivery peptides.

[0080] In certain instances, conjugation of a cationic ligand to oligonucleotides often results in improved resistance to nucleases. Representative examples of cationic ligands are propylammonium and dimethylpropylammonium. Interestingly, antisense oligonucleotides were reported to retain their high binding affinity to mRNA when the cationic ligand was dispersed throughout the oligonucleotide. See M. Manoharan *Antisense & Nucleic Acid Drug Development* 2002, 12, 103 and references therein.

[0081] The ligand-conjugated dsRNA of the invention may be synthesized by the use of a dsRNA that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the dsRNA. This reactive oligonucleotide may be reacted directly with commercially-available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto. The methods of the invention facilitate the synthesis of ligand-conjugated dsRNA by the use of, in some preferred embodiments, nucleotide monomers that have been appropriately conjugated with ligands and that may
further be attached to a solid-support material. Such ligand-nucleoside conjugates, optionally attached to a solid-support material, are prepared according to some preferred embodiments of the methods of the invention via reaction of a selected serum-binding ligand with a linking moiety located on the 5'-position of a nucleoside or oligonucleotide. In certain instances, a dsRNA bearing an aralkyl ligand attached to the 3'-terminus of the dsRNA is prepared by first covalently attaching a monomer building block to a controlled-pore glass support via a long-chain aminealkyl group. Then, nucleotides are bonded via standard solid-phase synthesis techniques to the monomer building-block bound to the solid support. The monomer building block may be a nucleoside or other organic compound that is compatible with solid-phase synthesis.

[0082] The dsRNA used in the conjugates of the invention may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioate and alkylated derivatives.

[0083] Teachings regarding the synthesis of particular modified oligonucleotides may be found in the following U.S. Pat. Nos. 5,138,045 and 5,218,105, drawn to polyamine conjugated oligonucleotides; U.S. Pat. No. 5,212,295, drawn to monomers for the preparation of oligonucleotides having chiral phosphorus linkages; U.S. Pat. Nos. 5,378,825 and 5,541,307, drawn to oligonucleotides having modified backbones; U.S. Pat. No. 5,386,023, drawn to backbone-modified oligonucleotides and the preparation thereof through reductive coupling; U.S. Pat. No. 5,457,191, drawn to modified nucleobases based on the 3-deazapurine ring system and methods of synthesis thereof; U.S. Pat. No. 5,459,255, drawn to modified nucleobases based on N-2 substituted purines; U.S. Pat. No. 5,521,302, drawn to processes for preparing oligonucleotides having chiral phosphorus linkages; U.S. Pat. No. 5,539,082, drawn to peptide nucleic acids; U.S. Pat. No. 5,554,746, drawn to oligonucleotides having β-lactam backbones; U.S. Pat. No. 5,571,302, drawn to methods and materials for the synthesis of oligonucleotides; U.S. Pat. No. 5,578,718, drawn to nucleosides having alkylthio groups, wherein such groups may be used as linkers to other moieties attached at any of a variety of positions of the nucleoside; U.S. Pat. Nos. 5,587,361 and 5,599,797, drawn to oligonucleotides having phosphorothioate linkages of high chiral purity; U.S. Pat. No. 5,506,351, drawn to processes for the preparation of 2′-O-alkyl guanosine and related compounds, including 2,6-diaminopurine compounds; U.S. Pat. No. 5,587,469, drawn to oligonucleotides having N-2 substituted purines; U.S. Pat. No. 5,587,470, drawn to oligonucleotides having 3-deazapurines; U.S. Pat. No. 5,223,168, and U.S. Pat. No. 5,608,046, both drawn to conjugated 4′-desmethyl nucleoside analogs; U.S. Pat. Nos. 5,602,240, and 5,610,289, drawn to backbone-modified oligonucleotide analogs; U.S. Pat. Nos. 6,262,241, and 5,459,255, drawn to, inter alia, methods of synthesizing 2′-fluoro-oligonucleotides.

[0084] In the ligand-conjugated dsRNA and ligand-molecule bearing sequence-specific linked nucleosides of the invention, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

[0085] When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. Oligonucleotide conjugates bearing a variety of molecules such as steroids, vitamins, lipids and reporter molecules, has previously been described (see Manoharan et al., PCT Application WO 93/07883). In a preferred embodiment, the oligonucleotides or linked nucleosides of the invention are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

[0086] The incorporation of a 2′-O-methyl, 2′-O-ethyl, 2′-O-propyl, 2′-O-allyl, 2′-O-aminoallyl or 2′-deoxy-2′-fluoro group in nucleosides of an oligonucleotide confers enhanced hybridization properties to the oligonucleotide. Further, oligonucleotides containing phosphorothioate backbones have enhanced nuclease stability. Thus, functionalized, linked nucleosides of the invention can be augmented to include either or both a phosphorothioate backbone or a 2′-O-methyl, 2′-O-ethyl, 2′-O-propyl, 2′-O-aminoallyl, 2′-O-allyl or 2′-deoxy-2′-fluoro group.

[0087] In some preferred embodiments, functionalized nucleoside sequences of the invention possessing an amino group at the 5′-terminus are prepared using a DNA synthesizer, and then reacted with an active ester derivative of a selected ligand. Active ester derivatives are well known to those skilled in the art. Representative active esters include N-hydrosuccinimide esters, tetrahydrophomolonic esters, pentfluorophomolonic esters and pentachlorophomolonic esters. The reaction of the amino group and the active ester produces an oligonucleotide in which the selected ligand is attached to the 5′-position through a linking group. The amino group at the 5′-terminus can be prepared utilizing a 5′-Amino-Modifier C6 reagent. In a preferred embodiment, ligand molecules may be conjugated to oligonucleotides at the 5′-position by the use of a ligand-nucleoside phosphoramidite wherein the ligand is linked to the 5′-hydroxy group directly or indirectly via a linker. Such ligand-nucleoside phosphoramidites are typically used at the end of an automated synthesis procedure to provide a ligand-conjugated oligonucleotide bearing the ligand at the 5′-terminus.

[0088] In one preferred embodiment of the methods of the invention, the preparation of ligand conjugated oligonucleotides commences with the selection of appropriate precursor molecules upon which to construct the ligand molecule. Typically, the precursor is an appropriately-protected derivative of the commonly-used nucleosides. For example, the synthetic precursors for the synthesis of the ligand-conjugated oligonucleotides of the invention include, but are not limited to, 2′-aminoalkoxy-5′-ODMT-nucleosides, 2′-6-aminoalkoxy-lamino-5′-ODMT-nucleosides, 3′-6-aminoalkoxy-2′-deoxy-nucleosides, 2′-6-aminoalkoxy-2′-protected-nucleosides, 3′-6-aminoalkoxy-5′-ODMT-nucleosides, and 3′-aminoalkoxy-lamino-5′-ODMT-nucleosides that may be protected in the nucleobase portion of the molecule. Methods for the synthe-
sis of such amino-linked protected nucleoside precursors are known to those of ordinary skill in the art. 

[0089] In many cases, protecting groups are used during the preparation of the compounds of the invention. As used herein, the term “protected” means that the indicated moiety has a protecting group appended thereon. In some preferred embodiments of the invention, compounds contain one or more protecting groups. A wide variety of protecting groups can be employed in the methods of the invention. In general, protecting groups render chemical functionalities inert to specific reaction conditions, and can be appended to and removed from such functionalities in a molecule without substantially damaging the remainder of the molecule. 


[0091] Examples of hydroxyl protecting groups include, but are not limited to, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy) ethyl, 2-trimethylsilylthethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, 2,6-dichlorobenzyl, diphenylmethyl, p,p’-dinitrobenzhydryl, p-nitrobenzyl, triphenylmethyl, trimethylsilyl, triethylsilyl, p-tolylmethyl, p-tolylsilyl, benzoylformate, acetate, chlорект, trichloracetate, trifluoroacetate, pivaloate, benzoate, p-phenylbenzoate, 9-fluorenylethyl carbonate, mesylate and tosylate. 


[0093] Additional amino-protecting groups include, but are not limited to, carbamate protecting groups, such as 2-trimethylsilyloxycarbonyl (Teoc), 1-methyl-1-(4-biphenylyl) ethoxycarbonyl (Boc), t-butoxycarbonyl (BOC), allyloxy-carbonyl (Alloc), 9-fluorenylethylxocarbonyl (Mfoc), and benzyloxycarbonyl (Cbz); amide protecting groups, such as formyl, acetyl, trihaloacetyl, benzoyl, and nitrophenylacetyl; sulfonamide protecting groups, such as 2-nitrobenzenesulfonic acid; and imine and cyclic imide protecting groups, such as phthalimido and dithiauccinyl. Equivalents of these amino-protecting groups are also encompassed by the compounds and methods of the invention. 

[0094] Many solid supports are commercially available and one of ordinary skill in the art can readily select a solid support to be used in the solid-phase synthesis steps. In certain embodiments, a universal support is used. A universal support allows for preparation of oligonucleotides having unusual or modified nucleotides located at the 3'-terminus of the oligonucleotide. Universal Support 500 and Universal Support II are universal supports that are commercially available from Glen Research, 2325 Davis Drive, Sterling, Va. For further details about universal supports see Scott et al., Innovations and Perspectives in solid-phase Synthesis, 3rd International Symposium, 1994, Ed. Roger Epton, Mayflower Worldwide, 115-124; Azhayev, A. V. Tetrahedron 1999, 55, 778-800; and Azhayev and Antipolsky Tetrahedron 2001, 57, 4977-4986. In addition, it has been reported that the oligonucleotide can be cleaved from the universal support under milder reaction conditions when oligonucleotide is bonded to the solid support via a syn-1,2-acetoxyphosphate group which more readily undergoes basic hydrolysis. See Guzov, A. I.; Manoharan, M. J. Am. Chem. Soc. 2003, 125, 2380. 

[0095] The nucleosides are linked by phosphorus-containing or non-phosphorus-containing covalent internucleoside linkages. For the purposes of identification, such conjugated nucleosides can be characterized as ligand-bearing nucleosides or ligand-nucleoside conjugates. The linked nucleosides having an arylalkyl ligand conjugated to a nucleoside within their sequence will demonstrate enhanced dsRNA activity when compared to like dsRNA compounds that are not conjugated. 

[0096] The arylalkyl-ligand-conjugated oligonucleotides of the invention also include conjugates of oligonucleotides and linked nucleosides wherein the ligand is attached directly to the nucleoside or nucleotide without the intermediary of a linker group. The ligand may preferably be attached, via linking groups, at a carboxyl, amino or oxo group of the ligand. Typical linking groups may be ester, amide or carbamate groups. 

[0097] Specific examples of preferred modified oligonucleotides envisioned for use in the ligand-conjugated oligonucleotides of the invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined here, oligonucleotides having modified backbones or internucleoside linkages include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of the invention, modified oligonucleotides that do not have a phosphorus atom in their interbase backbone can also be considered to be oligonucleosides. 

[0098] Specific oligonucleotide chemical modifications are described below. It is not necessary for all positions in a given compound to be uniformly modified. Conversely, more than one modifications may be incorporated in a single dsRNA compound or even in a single nucleotide thereof. 

[0099] Preferred modified internucleoside linkages or backbones include, for example, phosphorothioates, chiral phosphoroheptates, phosphorodithioates, phosphorotriesters, aminooalkylphosphorotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphonates, phosphoramidates including 3'-amino phosphoramidate and aminooalkylphosphoramidates, thionophosphoramidates, thionooalkylphosphonates, and boronophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free-acid forms are also included. 

[0100] Representative United States patents relating to the preparation of the above phosphorus-atom-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,833; 4,476,301; 5,023,245; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,466; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111;
Preferred modified internucleoside linkages or backbones that do not include a phosphorus atom therein (i.e., oligonucleosides) have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having phosphorino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfenate and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfinate backbones; methyleneimino and methylenehydrinazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S, and CH₂ component parts.

Representative United States patents relating to the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,663,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

In other preferred oligonucleotide mimetics, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleoside units are maintained with novel groups. The nucleoside units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligonucleotide, an oligonucleotide mimic, that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar–backbone of an oligonucleotide is replaced with an amide-containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to atoms of the amide portion of the backbone. The backbone of these oligonucleotides will be introduced herein. Further teaching of PNA compounds can be found in Nielsen et al., *Science*, 1991, 254, 1497.

Some preferred embodiments of the invention employ oligonucleosides with phosphorothioate linkages and oligonucleosides with heteroatomic backbones, and in particular, \( \text{CH}_2\text{N}^\text{H} \text{O} \text{CH}_2 \), \( \text{CH}_3\text{N}^\text{H} \text{O} \text{CH}_2 \), \( \text{CH}_3\text{N}^\text{H} \text{O} \text{CH}_2 \), \( \text{CH}_3\text{N}^\text{H} \text{O} \text{CH}_2 \), \( \text{CH}_3\text{N}^\text{H} \text{O} \text{CH}_2 \), \( \text{CH}_3\text{N}^\text{H} \text{O} \text{CH}_2 \), wherein the native phosphodiester backbone is represented as \( \text{O} \text{P} \text{O} \text{CH}_2 \text{CH}_2 \) of the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also provided are oligonucleotides having morpholinoborne backbone structures of the above referenced U.S. Pat. No. 5,034,506.

The oligonucleotides employed in the ligand-conjugated oligonucleotides of the invention may additionally or alternatively comprise nucleobase (often referred to in the art simply as “base”) modifications or substitutions. As used herein, “unmodified” or “natural” nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases include other synthetic and natural nucleobases, such as 5-methylcytosine (5-me-C), 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 uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thiouracil, 8-hydroxy and other 8-substituted adenosines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyl adenine, 8-aza guanine and 8-azadene, 7-deazaguanine and 7-deaz adenosine and 3-deazaguanine and 3-deaz adenine.

Further oligonucleotides include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in the Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, those disclosed by English et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, Antisense Research and Applications, pages 289-302, Crooke, S. T. and Leblum, B., ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligonucleotides of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynyl cytosine. 5-Methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C. (Id., pages 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-methoxyethyl sugar modifications.

Representative United States patents relating to the preparation of certain of the above-noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; and 5,808,027, all of which are hereby incorporated by reference.

In certain embodiments, the oligonucleotides employed in the ligand-conjugated oligonucleotides of the invention may additionally or alternatively comprise one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-S-, or N-alkyl, O-, S-, or N-alkenyl, or O, S- or N-alkynyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C\( _n \) alkyl or C\( _n \) alkynyl and alkynyl. Particularly preferred are O(\( \text{CH}_3 \))\( _n \)OH, \( \text{CH}_3 \), O(\( \text{CH}_2 \))\( _n \)OCH\( _3 \), O(\( \text{CH}_2 \))\( _n \)NH\( _2 \), O(\( \text{CH}_2 \))\( _n \)OH\( _2 \), O(\( \text{CH}_2 \))\( _n \)NH\( _2 \), O(\( \text{CH}_2 \))\( _n \)ONH\( _2 \), and O(\( \text{CH}_2 \))\( _n \)ON(\( \text{CH}_2 \))\( _m \)OH, where n and m are from 1 to about 10. Other preferred oligonucleotides comprise one of the following at the 2' position: C\( _{10} \) alkyl, substituted lower alkyl, alkynyl, aralkyl, O-alkyl or O-alkynyl, SH, SCH\( _2 \), OCN, Cl, Br, CN, CF\( _3 \), OCF\( _3 \), SOC\( _3 \), SO\( _2 \) CH\( _2 \), ONO\( _2 \), NO\( _2 \), NH\( _2 \), heterocycloalkyl, heterocycloalkyl, amidooxalamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy [\( \text{O} \text{CH}_2 \text{CH}_2 \text{OCH}_3 \)], also known as 2'-O(2-
methoxyethyl) or 2'-MOE [Martin et al., Helv Chim. Acta, 1995, 78, 486], i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethyloxyethylene, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in U.S. Pat. No. 6,127,533, filed on Jan. 30, 1998, the contents of which are incorporated by reference.

[0109] Other preferred modifications include 2'-methoxy (2'-O—CH₃), 2'-aminoproxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides.

[0110] As used herein, the term “sugar substituent group” or “2'-substituent group” includes groups attached to the 2'-position of the ribofuransol moiety with or without an oxygen atom. Sugar substituent groups include, but are not limited to, fluoro, O-alkyl, O-alkylaminooxy, O-alkylalkoxy, protected O-alkylamino, O-alkylaminooxy, O-alkyl imidazole and polyethers of the formula (O-alkyl)ₙ, wherein m is 1 to about 10. Preferred among these polyethers are linear and cyclic polyethylene glycols (PEGs), and (PEG)-containing substituent groups, such as crown ethers and those which are disclosed by Ouchi et al. (Drug Design and Discovery 1992, 9:93); Ravasio et al. (J. Org. Chem. 1991, 56:4329); and Delgado et al. (Critical Reviews in Therapeutic Drug Carrier Systems 1992, 9:249), each of which is hereby incorporated by reference in its entirety. Further sugar modifications are disclosed by Cook (Anti-pain Drug Design, 1991, 6:585-607), fluoroo, O-alkyl, O-alkylaminooxy, O-alkyl imidazole, O-alkylaminoxy, and alkyl amino substitution is described in U.S. Pat. No. 6,166,197, entitled “Oligomeric Compounds having Pyrimidine Nucleotide(s) with 2' and 5' Substitutions,” wherein by incorporated by reference in its entirety.

[0111] Additional sugar substituent groups amenable to the invention include 2'-SR and 2'-NR₂ groups, wherein each R is, independently, hydrogen, a protecting group or substituted or unsubstituted alkyl, alkenyl, or alkynyl. 2'-SR Nucleosides are disclosed in U.S. Pat. No. 5,670,633, hereby incorporated by reference in its entirety. The incorporation of 2'-SR monomer synths is disclosed by Hamm et al. (J. Org. Chem., 1997, 62:3415-3420), 2'-NR nucleosides are disclosed by Goettingen, M., J. Org. Chem., 1996, 61, 6273-6281, and Polushin et al., Tetrahedron Lett., 1996, 37, 3227-3230. Further representative 2'-substituent groups amenable to the invention include those having one of formula I or II:

\[
\begin{align*}
\text{I} & \quad \text{O} \quad \text{(CH₂)₄CH₃} \quad \text{(O)ₙ} \quad \text{E} \\
\text{II} & \quad \text{O} \quad \text{Z₁} \quad \text{Z₂} \quad \text{Z₃₄} \quad \text{Z₄} \\
\end{align*}
\]

[0112] Wherein,

[0113] E is C₅-C₁₀ alkyl, N(Q₃)(Q₄) or N—C (Q₃)(Q₄); each Q₃ and Q₄ is, independently, H, C₁-C₁₀ alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or un tethered conjugate group, a linker to a solid support; or Q₃ and Q₄, together, form a nitrogen protecting group or a ring structure optionally including at least one additional heteroatom selected from N and O;

[0114] q₁ is an integer from 1 to 10;

[0115] q₂ is an integer from 1 to 10;

[0116] q₂ is 0 or 1;

[0117] q₂ is 0, 1 or 2;

[0118] each Z₁, Z₂ and Z₃ is, independently, C₄-C₉ cycloalkyl, C₄-C₁₄ aryl or C₄-C₁₃ heterocyclic, wherein the heteroatom in said heterocyclic group is selected from oxygen, nitrogen and sulfur;

[0119] Z₄ is OM⁺, SM⁺, or N(M⁺)₂; each M' is, independently, H, C₁-C₈ alkyl, C₅-C₆ haloalkyl, C(B—NH)(N[M⁺]₂), C(═O)(N[M⁺]₂) or OC(═O)(N[M⁺]₂); M₂ is H or C₁-C₈ alkyl; and

[0120] Z₅ is C₅-C₁₀ alkyl, C₅-C₁₀ haloalkyl, C₅-C₁₀ alkynyl, C₅-C₁₀ aryl, N(Q₃)(Q₄), OQ₅, halo, S(Q₆) or CN.

[0121] Representative 2'-O-sugar substituent groups of formula I are disclosed in U.S. Pat. No. 6,172,209, entitled “Capped 2'-Oxyethoxy Oligonucleotides,” hereby incorporated by reference in its entirety. Representative cyclic 2'-O-sugar substituent groups of formula II are disclosed in U.S. Pat. No. 6,271,358, entitled “RNA Targeted 2'-Modified Oligonucleotides that are Conformationally Reorganized,” hereby incorporated by reference in its entirety.

[0122] Sugars having O-substitutions on the ribosyl ring are also amenable to the invention. Representative substitutions for ring O include, but are not limited to, S, C₂H₂, CH₂, and CH₂. See, e.g., Secrist et al., Abstract 21, Program & Abstracts, Tenth International Roundtable, Nucleosides, Nucleotides and their Biological Applications, Park City, Utah, Sep. 16-20, 1992.

[0123] Oligonucleotides may also have sugar mimetics, such as cyclobutyl moieties, in place of the pentofuranosyl sugar. Representative United States patents relating to the preparation of such modified sugars include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,446,786; 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; 5,658,873; 5,670,633; 5,700,920; and 5,859,221, all of which are hereby incorporated by reference.

[0124] Additional modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide. For example, one additional modification of the ligand-conjugated oligonucleotides of the invention involves chemically linking the oligonucleotide one or more additional non-ligand moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties, such as a cholesterol moiety (Lestinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053), a thioether, e.g., hexyl-5-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765), a thiocolesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saisoon-Behnoosha et al., EMBO J., 1991, 10, 111; Kabano et al., FEBS Lett., 1990, 259, 327; Svinarchuk et al., Biochimie, 1993, 75, 49), a phospholipid, e.g., dihexadearyl-rac-glycerol or triethanolammonium 1,2-di-O-hexadecyl-rac-glycerol-3-H-phosphonate (Manoharan et al., Tet-

[0125] Representative United States patents relating to the preparation of such oligonucleotide conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,255,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,141,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,857,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928; and 5,688,941, each of which is herein incorporated by reference.

[0126] The invention also includes compositions employing oligonucleotides that are substantially chiral pure with regard to particular positions within the oligonucleotides. Examples of substantially chiral pure oligonucleotides include, but are not limited to, those having phosphorothioate linkages that are at least 75% Sp or Rp (Cook et al., U.S. Pat. No. 5,587,361) and those having substantially chiral pure (Sp or Rp) alkylphosphonate, phosphoramidate or phosphotriester linkages (Cook, U.S. Pat. Nos. 5,212,295 and 5,521,302).


Representative United States patents that teach the preparation of such oligonucleotide conjugates have been listed above. Typical conjugation protocols involve the synthesis of oligonucleotides bearing an aminon linker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the oligonucleotide still bound to the solid support or following cleavage of the oligonucleotide in solution phase. Purification of the oligonucleotide conjugate by HPLC typically affords the pure conjugate.

In another embodiment, the molecular conjugation may be converted into a building block, such as a phosphoramidite, via an alcohol group present in the molecule or by attachment of a linker bearing an alcohol group that may be phosphorylated.

Importantly, each of these approaches may be used for the synthesis of ligand conjugated oligonucleotides. Ami- nolinked oligonucleotides may be coupled directly with ligand via the use of coupling reagents or following activation of the ligand as an NHS or penfluorophenolate ester. Ligand phosphoramidates may be synthesized via the attachment of an aminohexanol linker to one of the carboxyl groups followed by phosphorylation of the terminal alcohol functionality. Other linkers, such as steaamine, may also be utilized for conjugation to a chloroacetyl linker present on a synthesized oligonucleotide.

III. Pharmaceutical Compositions Comprising dsRNA

In one embodiment, the invention provides pharmaceutical compositions comprising a dsRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical composition comprising the dsRNA is useful for treating a disease or disorder associated with the expression or activity of the Nav1.8 gene, such as neuropathic or inflammatory pain.

In another embodiment, the invention provides pharmaceutical compositions comprising at least two dsRNAs, designed to target different regions of the Nav1.8 gene, and a pharmaceutically acceptable carrier. In this embodiment, the individual dsRNAs are prepared as described in the preceding section, which is incorporated by reference herein. One dsRNA can have a nucleotide sequence which is substantially complementary to at least one part of the Nav1.8 gene; additional dsRNAs are prepared, each of which has a nucleotide sequence that is substantially complementary to different part of the Nav1.8 gene. The multiple dsRNAs may be combined in the same pharmaceutical composition, or formulated separately. If formulated individually, the compositions containing the separate dsRNAs may comprise the same or different carriers, and may be administered using the same or different routes of administration. Moreover, the pharmaceutical compositions comprising the individual dsRNAs may be administered substantially simultaneously, sequentially, or at preset intervals throughout the day or treatment period.

The pharmaceutical compositions of the invention are administered in dosages sufficient to inhibit expression of the Nav1.8 gene. The present inventors have found that, because of their improved efficiency, compositions comprising the dsRNA of the invention can be administered at surprisingly low dosages. A maximum dosage of 5 mg dsRNA per kilogram body weight of recipient per day is sufficient to inhibit or completely suppress expression of the Nav1.8 gene, or alleviate chronic pain.

In general, a suitable dose of dsRNA will be in the range of 0.01 to 5.0 milligrams per kilogram body weight of
the recipient per day, preferably in the range of 0.1 to 200 micrograms per kilogram body weight per day, more preferably in the range of 0.1 to 100 micrograms per kilogram body weight per day, even more preferably in the range of 1.0 to 50 micrograms per kilogram body weight per day, and most preferably in the range of 1.0 to 25 micrograms per kilogram body weight per day. The pharmaceutical composition may be administered once daily, or the dsRNA may be administered as two, three, four, five, six or more sub-doses at appropriate intervals throughout the day or even using continuous infusion. In that case, the dsRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, e.g., using a conventional sustained release formulation which provides sustained release of the dsRNA over a several day period. Sustained release formulations are well known in the art. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

[0134] The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and in vivo half-lives for the individual dsRNAs encompassed by the invention can be made using conventional methodologies or on the basis of in vivo testing using an appropriate animal model, as described elsewhere herein.

[0135] Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as pain. Such models are used for in vivo testing of dsRNA, as well as for determining a therapeutically effective dose.

[0136] The pharmaceutical compositions encompassed by the invention may be administered by any means known in the art including, but not limited to oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, epidural, intrathecal, intracerebroventricular, intraparenchymal (within the peripheral or central nervous system), subcutaneous, transdermal, intranasal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration. In preferred embodiments, the pharmaceutical compositions are administered intrathecally by continuous infusion such as with a pump, or intrathecally by bolus injection. In other preferred embodiments, the pharmaceutical compositions are administered intravenously by continuous infusion such as with a pump, or intravenously by bolus injection.

[0137] For intrathecal, intracerebroventricular, intramuscular, intraparenchymal (within the peripheral or central nervous system), subcutaneous and intravenous use, the pharmaceutical compositions of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer’s solution and isotonic sodium chloride. In a preferred embodiment, the carrier consists exclusively of an aqueous buffer. In this context, “exclusively” means no auxiliary agents or encapsulating substances are present which might affect or mediate uptake of dsRNA in the cells that express the Nav1.8 gene. Such substances include, for example, micellar structures, such as liposomes or capsids, as described below. Surprisingly, the present inventors have discovered that compositions containing only naked dsRNA and a physiologically acceptable solvent are taken up by cells, where the dsRNA effectively inhibits expression of the Nav1.8 gene. Although microinjection, lipofection, viruses, viroids, capsids, capsoids, or other auxiliary agents are required to introduce dsRNA into cell cultures, surprisingly these methods and agents are not necessary for uptake of dsRNA in vivo. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

[0138] The pharmaceutical compositions useful according to the invention also include encapsulated formulations to protect the dsRNA against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyoxyethers, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811; PCT publication WO 91.06309; and European patent publication EP-A-43075, which are incorporated by reference herein.

[0139] Using the small interfering RNA vectors previously described, the invention also provides devices, systems, and methods for delivery of small interfering RNA to target locations in the nervous system and/or the brain. The envisioned route of delivery is through the use of implanted, indwelling, intrathecal, intracerebroventricular or intraparenchymal catheters that provide a means for injecting small volumes of fluid containing the dsRNA of the invention directly into local nerves or local brain tissue, or into bodily fluids surrounding these tissues. The proximal end of these catheters may be connected to an implanted, intrathecal or intracerebral access port surgically affixed to the patient’s body or cranium, or to an implanted drug pump located in the patient’s torso.

[0140] Alternatively, implantable delivery devices, such as an implantable pump may be employed. Examples of the delivery devices within the scope of the invention include the Model 8506 investigational device (by Medtronic, Inc. of Minneapolis, Minn.), which can be implanted subcutaneously in the body or on the cranium, and provides an access port through which therapeutic agents may be delivered to the nerves or brain. Delivery occurs through a stereotactically implanted polyurethane catheter. Two models of catheters that can function with the Model 8506 access port include the Model 8770 ventricular catheter by Medtronic, Inc., for delivery to the intracerebral ventricles, which is disclosed in U.S. Pat. No. 6,093,180, incorporated herein by reference, and the IPAI catheter by Medtronic, Inc., for delivery to the brain tissue itself (i.e., intraparenchymal delivery), disclosed in U.S. Ser. Nos. 09/540,444 and 09/625,751, which are incorporated herein by reference. The latter catheter has multiple outlets on its distal end to deliver the therapeutic agent to multiple sites along the catheter path. In addition to the aforementioned device, the delivery of the small interfering RNA
vectors in accordance with the invention can be accomplished with a wide variety of devices, including but not limited to U.S. Pat. Nos. 5,735,814, 5,814,014, and 6,042,579, all of which are incorporated herein by reference. Using the teachings of the invention and those of skill in the art will recognize that these and other devices and systems may be suitable for delivery of small interfering RNA vectors for the treatment of pain in accordance with the invention.

[0141] In one such embodiment, the method further comprises the steps of implanting a pump outside the body or brain, the pump coupled to a proximal end of the catheter, and operating the pump to deliver the predetermined dosage of the at least one small interfering RNA or small interfering RNA vector through the discharge portion of the catheter. A further embodiment comprises the further step of periodically refreshing a supply of at least one small interfering RNA or small interfering RNA vector to the pump outside said body or brain.

[0142] Thus, the invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Pat. Nos. 5,735,814 and 6,042,579, and further using a sensor as part of the infusion system to regulate the amount of small interfering RNA vectors delivered to the nerves or brain, like that taught in U.S. Pat. No. 5,814,014. Other devices and systems can be used in accordance with the method of the invention, for example, the devices and systems disclosed in U.S. Ser. Nos. 09/872,698 (filed Jun. 1, 2001) and 09/864,646 (filed May 23, 2001), which are incorporated herein by reference.

[0143] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit high therapeutic indices are preferred.

[0144] The data obtained from cell culture assays and animal studies can be used in formulation a range of dosage for use in humans. The dosage of compositions of the invention lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (e.g., achieving a decreased concentration of the polypeptide) that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0145] In addition to their administration individually or as a plurality, as discussed above, the dsRNAs of the invention can be administered in combination with other known agents effective in treatment of pain. In any event, the administering physician can adjust the amount and timing of dsRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

[0146] Methods for Treating Diseases Caused by Expression of the Nav1.8 Gene

[0147] In one embodiment, the invention provides a method for treating a subject having a pathological condition mediated by the expression of the Nav1.8 gene, such as neuropathic or inflammatory pain. In this embodiment, the dsRNA acts as a therapeutic agent for controlling the expression of the Nav1.8 protein. The method comprises administering a pharmaceutical composition of the invention to the patient (e.g., human), such that expression of the Nav1.8 gene is silenced. Because of their high specificity, the dsRNAs of the invention specifically target mRNAs of the Nav1.8 gene.

[0148] Pain

[0149] As used herein, the term “pain” is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term “pain” includes chronic pain such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and neuropathic pain. The term “pain” further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; and pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

[0150] “Neuropathic pain” refers to pain caused by injury or disease of the central or peripheral nervous system. In contrast to the immediate (acute) pain caused by tissue injury, neuropathic pain can develop days or months after a traumatic injury. Neuropathic pain frequently is long lasting or chronic, and is not limited in duration to the period of tissue repair. Neuropathic pain can occur spontaneously, or as a result of stimulation that normally is not painful. Neuropathic pain is caused by aberrant somatosensory processing, and is associated with chronic sensory disturbances, including spontaneous pain, hyperalgesia (i.e., sensation of more pain than the stimulus would warrant) and allodynia (i.e., a condition in which ordinarily painless stimuli induce the experience of pain). Neuropathic pain includes, but is not limited to, pain caused by peripheral nerve trauma, viral infection, diabetes mellitus, chemotherapy, causalgia, plexus-avulsion, spinal cord injury, neurona, limb amputation, vasculitis, nerve damage from surgery, nerve damage from chronic alcoholism, hypothyroidism, uremia, and vitamin deficiencies, among other causes. Neuropathic pain is one type of pain associated with cancer. Cancer pain can also be “nociceptive” or “mixed.”

[0151] “Chronic pain” can be defined as pain lasting longer than three months (Bonica, Semin. Anesth. 1986, 5:92-99), and may be characterized by unrelenting persistent pain that is not fully amenable to routine pain control methods. Chronic pain includes, but is not limited to, inflammatory pain, post-operative pain, cancer pain, osteoarthritis pain associated with metastatic cancer, chemotherapy-induced pain, trigeminal neuralgia, acute herpetic and post-herpetic neuralgia, diabetic neuropathy, pain due to arthritis, joint pain, myofascial pain, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, pain associated with spinal cord injury, multiple sclerosis, reflex sympathetic dystrophy and lower back pain and other forms of neuralgia, neuropathic, and idiopathic pain syndromes.

[0152] “Nociceptive pain” is due to activation of pain-sensitive nerve fibers, either somatic or visceral. Nociceptive pain is generally a response to direct tissue damage. The
initial trauma causes the release of several chemicals including bradykinin, serotonin, substance P, histamine, and prostaglandin. When somatic nerves are involved, the pain is typically experienced as an aching or pressure-like sensation.

In the phrase “pain and related disorders”, the term “related disorders” refers to disorders that either cause or are associated with pain, or have been shown to have similar mechanisms to pain. These disorders include addiction, seizure, stroke, ischemia, a neurodegenerative disorder, anxiety, depression, headache, asthma, rheumatic disease, osteoarthritis, retinopathy, inflammatory eye disorders, pruritis, ulcer, gastric lesions, uncontrollable urination, an inflammatory or unstable bladder disorder, inflammatory bowel disease, irritable bowel syndrome (IBS), irritable bowel disease (IBD), gastroesophageal reflux disease (GERD), functional dyspepsia, functional chest pain of presumed eosinophilic origin, functional dysphagia, non-cardiac chest pain, symptomatic gastroesophageal disease, gastritis, aerophagia, functional constipation, functional diarrhoea, burulence, chronic functional abdominal pain, recurrent abdominal pain (RAP), functional abdominal bloating, functional biliary pain, functional incontinence, functional ano-rectal pain, chronic pelvic pain, pelvic floor dyssteagia, unspecified functional ano-rectal disorder, cholecytisalgia, interstitial cystitis, dysmenorrhea, and dyspareunia.

The invention thus provides the use of an anti-Nav1.8 dsRNA administered to a human, particularly by intrathecal infusion or injection, or by intravenous infusion or injection, for the treatment of pain, including neuropathic and inflammatory pain.

The pharmaceutical compositions encompassed by the invention may be administered by any means known in the art including, but not limited to oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, epidural, intrathecal, intracerebroventricular, intraparenchymal (within the peripheral or central nervous system), subcutaneous, transdermal, intranasal, airway (aerosol), nasal, rectal, vaginal and topical (including buccal and sublingual) administration, and epidermal administration. In preferred embodiments, the pharmaceutical compositions are administered intrathecally by continuous infusion such as with a pump, or intrathecally by bolus injection. In other preferred embodiments, the pharmaceutical compositions are administered intravenously by continuous infusion such as with a pump, or intravenously by bolus injection.

Methods for Inhibiting Expression of the Nav1.8 Gene

In yet another aspect, the invention provides a method for inhibiting the expression of the Nav1.8 gene in a mammal. The method comprises administering a composition comprising a dsRNA, wherein the dsRNA comprises a nucleotide sequence which is complementary to at least a part of an RNA transcript of the Nav1.8 gene of the mammal to be treated. When the organism to be treated is a mammal such as a human, the composition may be administered by any means known in the art including, but not limited to oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, epidural, intrathecal, intracerebroventricular, intraparenchymal (within the peripheral or central nervous system), subcutaneous, transdermal, intranasal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration. In preferred embodiments, the compositions are administered by intrathecal infusion or injection, or by intravenous infusion or injection.

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

EXAMPLES

Example 1

Gene Walking of the Nav1.8 Gene

siRNAs were identified in a multi step sequence analysis process in order to design siRNAs targeting the Nav1.8 gene in 4 species of interest.

ChitalW multiple alignment function of BioEdit Sequence Alignment Editor (version 7.0.4.1) was used to generate a global alignment of human (NM_006514), mouse (NM_000913), rat (NM_017247) and dog (NM001003203) Nav1.8 mRNA sequences.

Conserved regions were identified by embedded sequence analysis function of the software. Conserved regions were defined as sequence stretches with a minimum length of 19 bases for all aligned sequences containing no internal gaps. Sequence positions of conserved regions were counted according to the human sequence.

The siRNA design web interface at Whitehead Institute for Biomedical Research was used to identify all potential siRNAs targeting the conserved regions as well as their respective off-target hits to sequences in the human, mouse and rat RefSeq database. siRNAs satisfying the crossreactivity criteria were selected out of the candidates pool and subjected to the software embedded off-target analysis. For this, all selected siRNAs were analyzed in 3 rounds by the NCBI blast algorithm against the NCBI human, mouse and rat RefSeq database.

Blast results were downloaded and analyzed by a perl script in order to extract the identity of the best off-target hit for the antisense strand as well as the positions of occurring mismatches.

All siRNA candidates were ranked according to predicted properties. For this, different criteria were applied in order to identify siRNAs with the following properties:

- Reactivity criterion: targeting human, mouse, rat and dog sequences
- Specificity criterion: highly specific for human, at least specific for rat and mouse

The 2 siRNAs that satisfied the applied criteria were referred to as “multi-species targeting siRNAs”.

In order to identify more siRNAs a second round of siRNA identification steps were conducted correspondingly.
with additional regions that had been previously eliminated due to missing reactivity with dog sequences.

[0170] The resulting pool of 10 siRNAs matching the above-mentioned criteria were referred to as ‘human/rat/mouse targeting siRNAs’.

[0171] A third round of the siRNA design process was conducted while disregarding cross-reactivity to mouse.

[0172] All candidate siRNAs were again extracted and ranked in 3 steps according to the following criteria:

[0173] Step 1:
  [0174] reactivity criterium: targeting human, rat and mouse sequences
  [0175] specificity criterium: highly specific for human and rat, moderately specific for mouse
  [0176] \( \Rightarrow \) 4 siRNAs (added to pool of ‘human/rat/mouse targeting siRNAs’)

[0177] Step 2:
  [0178] reactivity criterium: targeting human and rat sequences
  [0179] sequence-embedded criterium: absence of stretches with more than 3 Gs in a row
  [0180] specificity criterium: highly specific for human
  [0181] \( \Rightarrow \) 19 siRNAs

[0182] Step 3:
  [0183] reactivity criterium: targeting human and rat sequences
  [0184] specificity criterium: highly specific for rat, specific for human and favorable doG value
  [0185] \( \Rightarrow \) 1 siRNA

[0186] The pool resulting from steps 2 and 3 (20 siRNAs) were referred to as ‘human/rat targeting siRNAs’.

[0187] In silico selected 36 siRNAs were synthesized (Table 1).

[0188] Additional sequence selections were performed using the above generalized methods except that cross-reactivity between species was not used as a selection criterium: the sequence selection was based solely on the human Nav1.8 sequence. In addition, ranking was based on off-target scores based on the closest FASTA hit as was as the number of potential off target genes. These siRNAs are provided in Table 4.

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### TABLE 1-continued

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### TABLE 4

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<th>SEQ ID activity [% of controls]</th>
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<td>SEQ ID Activity % of Controls</td>
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<td>524 ± 33</td>
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</table>
### Example 2

Optimization of siRNAs by Chemical Modification

As has been experienced by those working in the antisense field, ribonucleic acids are often quickly degraded by a range of nucleases present in virtually all biological environments, e.g. endonucleases, exonucleases etc. This vulnerability may be circumvented by chemically modifying these oligonucleotides such that nucleases may no longer attack. Consequently, siRNAs in Table 1 represent chemically modified oligonucleotides; these chemically modified siRNAs were tested for inhibitory activity on Nav1.8 gene expression (Nav1.8 mRNA levels).

<table>
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<tr>
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<th>Sense strand sequence (5’-3’)</th>
<th>Seq ID Antisense strand sequence NO. (5’-3’)</th>
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<td>537uaucuagugacucuaugcTT</td>
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<td>540 20 ± 5</td>
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<td>AD-11403</td>
<td>aguagggcagcaagucgcuTT</td>
<td>541gggcumacacuacucuacuTT</td>
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</table>

Further siRNAs specific for Nav1.8

Optimization of siRNAs by Chemical Modification

[0189] As has been experienced by those working in the antisense field, ribonucleic acids are often quickly degraded by a range of nucleases present in virtually all biological environments, e.g. endonucleases, exonucleases etc. This vulnerability may be circumvented by chemically modifying these oligonucleotides such that nucleases may no longer attack. Consequently, siRNAs in Table 1 represent chemically modified oligonucleotides; these chemically modified siRNAs were tested for inhibitory activity on Nav1.8 gene expression (Nav1.8 mRNA levels).

[0190] dsRNA Synthesis

[0191] Source of Reagents

[0192] Where the source of a reagent is not specifically given herein, such reagent may be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

[0193] siRNA Synthesis

[0194] Single-stranded RNAs were produced by solid phase synthesis on a scale of 1 μmole using an Expedite 8909 synthesizer (Applied Biosystems, Applera Deutschland GmbH, Darmstadt, Germany) and controlled pore glass (CPG, 500A, Proligo Biochemie GmbH, Hamburg, Germany) as solid support. RNA and DNA containing 2’-O-methyl nucleotides were generated by solid phase synthesis employing the corresponding phosphoramidites and 2’-O-methyl phosphoramidites, respectively (Proligo Biochemie GmbH, Hamburg, Germany). These building blocks were incorporated at selected sites within the sequence of the oligoribonucleotide chain using standard nucleoside phosphoramidite chemistry such as described in Current protocols in nucleic acid chemistry, Beaucage, S. L., et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA. Phosphorothioate linkages were introduced by replacement of the iodine oxidizer solution with a solution of the Beaucage reagent (Chruachem Ltd., Glasgow, UK) in acetonitrile (1%). Further ancillary reagents were obtained from Mallinckrodt Baker (Griesheim, Germany).

[0195] Deprotection and purification of the crude oligonucleotides by anion exchange HPLC were carried out according to established procedures. Yields and concentrations were determined by UV absorption of a solution of the respective RNA at a wavelength of 260 nm using a spectrophotometer (DU 640B, Beckman Coulter GmbH, Unterschleißheim, Germany). Double stranded RNA was generated by mixing an equimolar solution of complementary strands in annealing buffer (20 mM sodium phosphate, pH 6.8; 100 mM sodium chloride), heated in a water bath at 85-90°C for 3 minutes and cooled to room temperature over a period of 3-4 hours. The annealed RNA solution was stored at -20°C until use.

[0196] For the synthesis of 3’-cholesterol-conjugated siRNAs (herein referred to as -Chol or -sChol, depending on whether the link to the cholesterol group is effected via a phosphodiester or a phosphorothioate diester group), an appropriately modified solid support was used for RNA synthesis. The modified solid support was prepared as follows:

Diethyl-2-azabutane-1,4-dicarboxylate AA

[0197]

[0198] A 4.7 M aqueous solution of sodium hydroxide (50 mL) was added into a stirred, ice-cooled solution of ethyl glycinic acid hydrochloride (32.19 g, 0.23 mole) in water (50
mL). Then, ethyl acrylate (23.1 g, 0.23 mole) was added and the mixture was stirred at room temperature until completion of the reaction was ascertained by TLC. After 19 h the solution was partitioned with dichloromethane (3×100 mL). The organic layer was dried with anhydrous sodium sulfate, filtered and evaporated. The residue was distilled to afford AA (28.8 g, 61%).

3-[(Ethoxycarbonylmethyl]-[6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoyl]-amino]-propionic acid ethyl ester AB

Fmoc-6-amino-hexanoic acid (9.12 g, 25.83 mmol) was dissolved in dichloromethane (50 mL) and cooled with ice. Disopropylethylamine (3.25 g, 3.99 mL, 25.83 mmol) was added to the solution at 0°C. It was then followed by the addition of Diethyl-acetamide-1,4-dicarboxylate (5 g, 24.6 mmol) and dimethylamino pyridine (0.305 g, 2.5 mmol). The solution was brought to room temperature and stirred further for 6 h. Completion of the reaction was ascertained by TLC. The reaction mixture was concentrated under vacuum and ethyl acetate was added to precipitate disopropyl urea. The suspension was filtered. The filtrate was washed with 5% aqueous hydrochloric acid, 5% sodium bicarbonate and water. The combined organic layer was dried over sodium sulfate and concentrated to give the crude product which was purified by column chromatography (50% EtOAc/Hexanes) to yield 11.87 g (88%) of AB.

3-[(6-Amino-hexanoyl)-ethoxycarbonylmethyl]-amino]-propionic acid ethyl ester AC

[0201]

The hydrochloride salt of 3-[(6-Amino-hexanoyl)-ethoxycarbonylmethyl]-amino]-propionic acid ethyl ester AC (4.7 g, 14.8 mmol) was taken up in dichloromethane. The suspension was cooled to 0°C on ice. To the suspension diisopropylethylamine (3.87 g, 5.2 mL, 30 mmol) was added. To the resulting solution cholesteryl chloroformate (6.675 g, 14.8 mmol) was added. The reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane and washed with 10% hydrochloric acid. The product was purified by flash chromatography (10.3 g, 92%).

[0204]
Potassium t-butoxide (1.1 g, 9.8 mmol) was slurried in 30 mL of dry toluene. The mixture was cooled to 0°C on ice and 5 g (6.6 mmol) of diester AD was added slowly with stirring within 20 mins. The temperature was kept below 5°C during the addition. The stirring was continued for 30 mins at 0°C and 1 mL of glacial acetic acid was added, immediately followed by 4 g of NaH$_2$PO$_4$·H$_2$O in 40 mL of water. The resultant mixture was extracted twice with 100 mL of dichloromethane each and the combined organic extracts were washed twice with 10 mL of phosphate buffer each, dried, and evaporated to dryness. The residue was dissolved in 60 mL of toluene, cooled to 0°C, and extracted with three 50 mL portions of cold pH 9.5 carbonate buffer. The aqueous extracts were adjusted to pH 3 with phosphoric acid, and extracted with five 40 mL portions of chloroform which were combined, dried and evaporated to dryness. The residue was purified by column chromatography using 25% ethylacetate/hexane to afford 1.9 g of b-ketoester (39%).

Methanol (2 mL) was added dropwise over a period of 1 h to a refluxing mixture of b-ketoester AE (1.5 g, 2.2 mmol) and sodium borohydride (0.226 g, 6 mmol) in tetrahydrofuran (10 mL). Stirring was continued at reflux temperature for 1 h. After cooling to room temperature, 1 N HCl (12.5 mL) was added, the mixture was extracted with ethylacetate (3×40 mL). The combined ethylacetate layer was dried over anhydrous sodium sulfate and concentrated under vacuum to yield the product which was purified by column chromatography (10% MeOH/CHCl$_3$) (89%).
Diol AF (1.25 g, 1.994 mmol) was dried by evaporating with pyridine (2×5 mL) in vacuo. Anhydrous pyridine (10 mL) and 4,4’-dimethoxytrityl chloride (0.724 g, 2.13 mmol) were added with stirring. The reaction was carried out at room temperature overnight. The reaction was quenched by the addition of methanol. The reaction mixture was concentrated under vacuum and to the residue dichloromethane (50 mL) was added. The organic layer was washed with 1M aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residual pyridine was removed by evaporating with toluene. The crude product was purified by column chromatography (2% MeOH/Chloroform, Rf=0.5 in 5% MeOH/CHCl₃) (1.75 g, 95%).

Succinic acid mono-(4-[bis-(4-methoxy-phenyl)-phenyl-methoxymethyl]-1-{6-[17-(1,5-dimethyl-hexyl)-10,13-dimethyl 2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[al]phenanthren-3-yl]oxyxycarbonylaminol]-hexanoyl}-pyrrolidin-3-yl) ester AH

The crude product was purified by column chromatography (2% MeOH/Chloroform, Rf=0.5 in 5% MeOH/CHCl₃) (1.75 g, 95%).
[0212] Compound AG (1.0 g, 1.05 mmol) was mixed with succinic anhydride (0.150 g, 1.5 mmol) and DMAP (0.073 g, 0.6 mmol) and dried in a vacuum at 40°C overnight. The mixture was dissolved in anhydrous dichloroethane (3 mL), triethylamine (0.318 g, 0.440 mL, 3.15 mmol) was added and the solution was stirred at room temperature under argon atmosphere for 16 h. It was then diluted with dichloromethane (40 mL) and washed with ice cold aqueous citric acid (5 wt%, 30 mL) and water (2×20 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was used as such for the next step.

[0213] Cholesterol Derivatised CPG AI

![Chemical structure](image)

[0214] Succinate AH (0.254 g, 0.242 mmol) was dissolved in a mixture of dichloromethane/acetonitrile (3:2, 3 mL). To that solution DMAP (0.0296 g, 0.242 mmol) in acetonitrile (1.25 mL), 2,2'-Dithio-his(5-nitropyridine) (0.075 g, 0.242 mmol) in acetonitrile/dichloromethane (3:1, 1.25 mL) were added successively. To the resulting solution triphenylphosphine (0.064 g, 0.242 mmol) in acetonitrile (0.6 mL) was added. The reaction mixture turned bright orange in color. The solution was agitated briefly using a wrist-action shaker (5 mins). Long chain alkyl amine-CPG (LCAA-CPG) (1.5 g, 61 mM) was added. The suspension was agitated for 2 h. The CPG was filtered through a sintered funnel and washed with acetonitrile, dichloromethane and ether successively. Unreacted amino groups were masked using acetic anhydride/pyridine. The achieved loading of the CPG was measured by taking UV measurement (37 mM/g).

[0215] The synthesis of siRNAs bearing a 5′-12-deca-canoic acid bisdeeylamid group (herein referred to as “5′-C32”) or a 5′-cholesterol derivative group (herein referred to as “5′-Chol.”) was performed as described in WO 2004/065601, except that, for the cholesterol derivative, the oxidation step was performed using the Beaucage reagent in order to introduce a phosphorothioate linkage at the 5′-end of the nucleic acid oligomer.

[0216] Nucleic acid sequences are represented below using standard nomenclature, and specifically the abbreviations of Table 2.

### TABLE 2

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<th>Nucleotide(s)</th>
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</tr>
<tr>
<td>c</td>
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### TABLE 2-continued

<table>
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</tr>
<tr>
<td>T, t</td>
<td>2′-deoxy-thymidine-3′-phosphate, thymidine-3′-phosphate</td>
</tr>
<tr>
<td>U, u</td>
<td>2′-deoxy-uridine-5′-phosphate, uridine-5′-phosphate</td>
</tr>
</tbody>
</table>

*capital letters represent 2′-deoxyribonucleotides (DNA); lower case letters represent ribonucleotides (RNA)*

[0217] Single-Dose Screen of Nav1.8 siRNAs Against mRNA Expression of Transfected Human Nav1.8 in Cos-7 Cells.

[0218] All Nav1.8 siRNAs in Table 1 and Table 4 were tested initially at a single dose of 100 nM (Table 1) or 50 nM (Table 4) for activity in reducing mRNA expression of transfected human Nav1.8 in Cos-7 cells. One day before transfection, Cos-7 cells (D8MZ, Braunschweig, Germany) were seeded at 1.5x10⁴ cells/well on 96-well plates (Greiner Bio-One GmbH, Frickenhausen, Germany) in 100 μL of growth medium (Dulbecco’s MEM, 10% fetal calf serum, 2 mM L-glutamine, 1.2 μg/mL sodium bicarbonate, 100 units penicillin/
100 µg/ml streptomycin, all from Biochrom AG, Berlin, Germany). Four hours prior to siRNA transfection, 20 ng of plasmid/well (Table 1) or 50 ng/well (Table 4) were transfected with Lipofectamine-2000 (Invitrogen) as described below for the siRNAs, with the plasmid diluted in Opti-MEM to a final volume of 12.5 µl/well, prepared as a mastermix for the whole plate.

[0219] siRNA transfections were performed in triplicate. For each well, 0.5 µl Lipofectamine2000 (Invitrogen GmbH, Karlsruhe, Germany) was mixed with 12 µl Opti-MEM (Invitrogen) and incubated for 15 min at room temperature. For an siRNA concentration of 100 nM in a transfection volume of 100 µl, 2 µl of a 5 µM siRNA were mixed with 10.5 µl Opti-MEM per well, combined with the Lipofectamine2000-Opti-MEM mixture and again incubated for 15 minutes at room temperature. During that incubation time, growth medium was removed from cells and replaced by 75 µl/well of fresh medium. In six wells, growth medium was replaced by 100 µl of fresh medium and cells were lysed immediately by adding lysis mixture, as described below, in order to analyse the background value in the bDNA-assay caused by the Nav1.8-cDNA in the plasmid. siRNA-Lipofectamine2000-complexes were applied completely (25 µl each per well) to the cells and cells were incubated for 24 h at 37°C and 5% CO2 in a humidified incubator (Heraeus GmbH, Hanau, Germany).

[0220] Cells were harvested by applying 50 µl of lysis mixture (from the QuantiGene bDNA-kit from Genospexa, Fremont, USA) to each well and were lysed at 53°C for 30 min. Afterwards, 50 µl of the lysates were incubated with probesets specific to human Nav 1.8 and human GAPDH (sequence of probesets see below) and processed according to the manufacturer’s protocol for QuantiGene. Chemoluminescence was measured in a Victor2-Light (Perkin Elmer, Wiesbaden, Germany) as RLUs (relative light units) and values obtained with the human Nav 1.8 probeset were normalized to the respective human GAPDH (GAPDH sequence of Cercopithecus aethiops so far unknown) values for each well. Values obtained with cells lysed 4 h after plasmid transfection were subtracted from the values obtained with cells lysed 24 h after siRNA transfection. Values acquired with siRNAs directed against Nav1.8 were further normalized relative to the value obtained with an unrelated siRNA (directed against hepatitis C virus) which was set to 100%.

[0221] FIG. 1 provides the results from a representative experiment where siRNAs from Table 1 were tested at a single dose of 100 nM and Table 4 provides the results for additional siRNAs at a dose of 50 nM. Several siRNAs (in Tables 1 and 4) were effective at the dose tested in reducing Nav1.8 mRNA levels by at least 50% in COS-7 cells transfected with Nav1.8.

[0222] Dose-Response Curves for Selected siRNAs Against mRNA Expression of Transfected Human Nav 1.8 in COS-7 Cells

[0223] Several effective siRNAs against Nav1.8 from the single dose screen (results in FIG. 1) were further characterized by dose response curves. For dose response curves, transfections were performed as for the single dose screen above, but with the following concentrations of siRNA (nM): 100, 33, 11, 3.7, 1.2, 0.4, 1, 0.14, 0.05, 0.015, 0.005 and mock (no siRNA). siRNAs were diluted with Opti-MEM to a final volume of 12.5 µl according to the above protocol.

[0224] Three independent dose response experiments were carried out to generate dose response curves (DRCs). The dose response curves were repeated, and a summary of the results are provided in Table 3.

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[0225] Specificity Testing of the Nav1.8 siRNAs Against Nav1.5 mRNA

[0226] Nav1.5 is an NaV subtype that is closely related to Nav1.8, but has an important role in normal cardiac function. Therefore, it is important to confirm that siRNAs selective for Nav1.8 do not inhibit Nav1.5 expression. Several siRNAs were tested for specificity towards Nav1.8 by transfecting SW620 cells, which express endogenous human Nav1.5, with these siRNAs, and assessing Nav1.5 mRNA levels. A control unrelated siRNA (AL-DP-5002) was also transfected into SW620 cells. siRNAs targeting Nav1.8 were tested at the following doses: 1200 nM, 400 nM, 133.3 nM, 44.4 nM, 14.8 nM, 4.9 nM, 1.6 nM, and mock (without siRNA). One siRNA targeting Nav1.8 (AL-DP-6217) was tested at 1 nM, 10 nM, 100 nM and 1 µM. The expression of Nav1.5 mRNA, which encodes the protein with the highest homology to Nav1.8 in the Nav-family, was then quantified.

[0227] One day before transfection, SW620 cells (LCG Promocells, Wiesbaden, Germany) were seeded at 1.5x10⁴ cells/well on 96-well plates (Greiner Bio-One GmbH, Frickenhausen, Germany) in 100 µl of growth medium (Leibowitz L-15 Medium, 10% fetal calf serum, 2 mM L-glutamine, 100 µg penicillin/100 µg streptomycin, all from Biochrom AG, Berlin, Germany).

[0228] siRNA transfections were performed in triplicate. For each well, 0.6 µl Oligofectamine (Invitrogen GmbH, Karlsruhe, Germany) was mixed with 2.4 µl Opti-MEM (Invitrogen) and incubated for 10 min at room temperature. For an siRNA concentration of 1200 nM in 100 µl transfection volume, 5 µl of 24 µM siRNA was mixed with 12 µl Opti-MEM per well, combined with the Oligofectamine-Opti-MEM mixture and again incubated for 20 minutes at room temperature. During that incubation time, growth medium was removed from cells and replaced by 80 µl/well of fresh growth medium without serum. siRNA-Oligofectamine-complexes were applied completely (20 µl each per well) to the cells and cells were incubated for 24 h at 37°C, without CO2 in a humidified incubator (Heraeus GmbH, Hanau, Germany).

[0229] Cells were harvested by applying 50 µl of lysis mixture (content of the QuantiGene bDNA-kit from Genospexa, Fremont, USA) to each well and were lysed at 53°C for 30 min. Afterwards, 50 µl of the lysates were incubated with probesets specific to human Nav1.5 and human GAPDH (sequence of probesets see below) and processed according to the manufacturer’s protocol for QuantiGene. Chemoluminescence was measured in a Victor2-Light (Perkin Elmer, Wiesbaden, Germany) as RLUs (relative light units) and values
obtained with the human Nav1.5 probeset were normalized to the respective human GAPDH values for each well. An unrelated control siRNA (directed against hepatitis C virus) was used as a negative control.

[0230] FIG. 2 provides the results. At the concentrations tested, the selected siRNAs targeting Nav1.8, did not exhibit significant dose-dependent inhibition of Nav1.5 mRNA as compared with the unrelated control siRNA (AL-DP-5002), confirming the specificity of these Nav1.8 siRNAs for Nav1.8 over Nav1.5. In addition, at concentrations up to 1 μM, AL-DP-6217 exhibited no significant inhibition of Nav1.5 mRNA (data not shown), confirming the specificity of this Nav1.8 siRNA for Nav1.8 over Nav1.5.

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[0232] Single-Dose Screen of Nav1.8 siRNAs Against mRNA Expression of Endogenous Nav1.8 in Primary Cultures of Rat Dorsal Root Ganglion Cells.

[0233] To confirm and extend the results obtained on mRNA expression of transfected human Nav1.8 in Cos-7 cells, Nav1.8 siRNAs from Table 1 were tested at a single dose of 200 nM for activity in reducing mRNA expression of endogenous Nav1.8 in primary cultures of rat dorsal root ganglion (DRG) cells.

[0234] DRG cells were isolated from Sprague-Dawley rats at postnatal day 3 to 6. DRGs were dissected and cells dissociated into single cells by incubation with 0.2% Wunsch units/ml Liberase Blendzyme (Roche) in S-MEM (Gibco) at 37° C. for 35 min. The cell suspension was pre-plated on tissue-culture plates to remove non-neuronal cells. Neurons were then plated onto tissue-culture Biocoat™ PDL Poly-D-Lysine/Laminin 96-well plates (BD Biosciences, Bedford Mass., USA) in F12-HAM’s Medium containing glutamine (Invitrogen Gibco, Carlsbad Calif., USA) with 5% fetal bovine serum (FBS, heat inactivated) and 5% horse serum (heat inactivated) (both Invitrogen Gibco, Carlsbad Calif., USA) supplemented with 50 ng/ml mouse nerve growth factor (NGF; Promega Corp., Madison Wis., USA) and kept at 37° C., 5% CO₂ in a humidified incubator until transfection.

[0235] Nav1.8 siRNAs were screened in DRG cultures at 200 nM in duplicate using TransMessenger™ Transfection reagent (Qiagen GmbH, Hilden, Germany, cat. no. 301525) which is based on a lipid formulation, a specific RNA-condensing reagent (Enhancer R™) and an RNA-condensing buffer (Buffer EC-R™), keeping siRNA:Enhancer R™ ratio (μg/μl) constant at 1:2, and siRNA:TransMessenger™ ratio (μg/μl) constant at 1:12.

[0236] DRG neurons were transfected 24 h post-plating. For each well, 0.52 μL Enhancer R™ were first mixed with 13.68 μL Buffer EC-R™ 0.8 μL of a 25 μM solution of AL-DP-5987 (0.26 μg) in annealing buffer (20 mM sodium phosphate, pH 6.8; 100 mM sodium chloride), or 0.8 μL of annealing buffer (siRNA-free control) were added and the mixture incubated for 5 min at RT. 3.12 μL TransMessenger™ Transfection Reagent were diluted with 6.88 μL Buffer EC-R™, added to the mixture, and the mixture incubated for another 10 min at room temperature to allow transfection-complex formation. 75 μL serum free F12-HAM’s Medium containing glutamine (Invitrogen Gibco, Carlsbad Calif., USA) supplemented with 50 ng/ml NGF 2.5S (Promega Corp., Madison Wis., USA) and 1:50 B27 supplement (Invitrogen Gibco, Carlsbad Calif., USA) were added to the transfection complexes and complete mixing achieved by gently pipetting up and down. The growth medium was removed from the DRG cells, and 90 μL of the above transfection complex mixture were added onto the cells. After 7 to 8 h of incubation at 37° C., 5% CO₂ in a humidified incubator supernatant was removed from the cells, fresh F12-HAM’s medium containing glutamine supplemented with 5% FBS, 5% horse serum (both Invitrogen Gibco, Carlsbad Calif., USA), 50 ng/ml mouse NGF 2.5S (Promega Corp., Madison Wis., USA) and 1:100 Penicillin/Streptomycin (Invitrogen Gibco, Carlsbad Calif., USA) was added, the cells were incubated for another 16 h at 37° C., 5% CO₂ in a humidified incubator, and Nav1.8 mRNA was quantified.

[0237] Nav1.8 mRNA levels were measured using the QuantiGene™ bDNA kit (Genospectra, Fremont, USA) according to manufacturer’s protocol. Briefly, the supernatant was removed from the DRG cells, and the cells were lysed by addition of 150 μL of Lysis Working Reagent (1 volume of Lysis Mixture plus 2 volumes of medium) and incubation at 52° C. for 30 min. 40 μL of the lysates were incubated at 52° C. for 40 min with the probe sets specific to rat Nav1.8 and mouse synuclein (SNCL). Chemiluminescence was read on a Victor2-Light™ (PerkinElmer Life And Analytical Sciences, Inc., Boston Mass., USA) as Relative Light Units (RLU). RLU for Nav1.8 were normalized to SNCL RLU for each well. Normalized Nav1.8/SNCL ratios were then compared to the siRNA-free control, which was set as 100%.

[0238] Fig. 3 provides the results. At 200 nM, at least 13 (indicated by **) of the Nav1.8 siRNAs tested showed at least 50% Nav1.8 mRNA knockdown compared to the siRNA-free control (TransMessenger™ only; **), while an unrelated control siRNA against RhoA had no effect.

[0239] Dose Response of dsRNA AL-DP-6209 Against mRNA Expression of Endogenous Nav1.8 in Primary Cultures of Rat Dorsal Root Ganglion Cells

[0240] One effective siRNA (AL-DP-6209) against Nav1.8 from the single dose screen in primary cultures of rat dorsal root ganglion cells was further characterized for dose dependence. For the dose response curve, experiments were performed as for the single dose screen in DRG cultures above, but with the following concentrations of siRNA: 175, 88, 44, 22, 11 and 5.5 nM. For all siRNA concentrations, siRNA: Enhancer R ratio (μg/μl) was kept constant at 1:2 and siRNA: TransMessenger ratio (μg/μl) was kept constant at 1:12 (Fig. 4).

[0241] Fig. 4 provides the result for the selected siRNA AL-DP-6209 from a dose response experiment. At 5.5 and 11 nM, AL-DP-6209 did not inhibit Nav1.8 mRNA expression relative to SNCL, whereas at 88 and 175 nM, AL-DP-6209 inhibited Nav1.8 mRNA expression relative to SNCL by >40%. Maximal inhibition of Nav1.8 mRNA expression relative to SNCL occurred in this experiment at 175 nM.
Intrathecal Bolus Administration of siRNAs Against Nav1.8 with iEECT Prevents Inflammatory Pain

The effect of siRNAs against Nav1.8, formulated with iEECT, on complete Freund’s adjuvant-induced tactile hypersensitivity was evaluated in rats (FIG. 5). Adult male Sprague-Dawley rats received an injection of CFA (150 μl) into the hindpaw on day 0. siRNAs against Nav1.8 were then administered by intrathecal bolus to the lumbar region of the spinal cord on days 1, 2 and 3; specifically, for each bolus injection, 2 μg of siRNA was complexed with iEECT transfection reagent (Neuromics, Minneapolis Minn., USA) at a ratio of 1:4 (w:v) in a total volume of 10 μl. Five groups of rats (with 5 rats per group) were treated with either siRNA (AL-DP-6049, AL-DP-6209, AL-DP-6217 or AL-DP-6218; Table 1), or PBS, in the presence of iEECT. Tactile hypersensitivity was expressed as tactile withdrawal thresholds which were measured by probing the hindpaw with 8 calibrated von Frey filaments (Stoelting, Wood Dale Ill., USA) (0.41 g to 15 g). Each filament was applied to the planar surface of the paw. Withdrawal threshold was determined by sequentially increasing and decreasing the stimulus strength and calculated with a Dixon non-parametric test (see Dixon, W. J. (1980) “Efficient analysis of experimental observations” Annu Rev Pharmacol Toxicol 20:441-462; Chaplan, S.R., F. W. Bach, et al.(1994)”Quantitative assessment of tactile alldynia in the rat paw” J Neurosci Methods 53:55-63). Tactile thresholds were measured before CFA injection to assess baseline thresholds, and then on day 4 after CFA and treatment with test articles. In rats treated with PBS, tactile hypersensitivity was pronounced on day 4, as evidenced by reduced paw withdrawal threshold, as expected. In rats treated with AL-DP-6209, tactile thresholds were nearly normalized on day 4, demonstrating that the Nav1.8 siRNA, AL-DP-6209, is efficacious in vivo against inflammation-induced hyperalgesia. Treatment with the Nav1.8 siRNA, AL-DP-6217, resulted in the average tactile threshold trending towards baseline, with one of five rats demonstrating a normal tactile response. AL-DP-6049 and AL-DP-6218 did not significantly alter tactile thresholds compared to PBS treatment, in this experimental paradigm.

These results demonstrate that siRNAs targeting Nav1.8, formulated with transfection reagent and administered intrathecally, alleviate CFA-induced tactile hyperalgesia, and therefore represent a novel approach to providing effective treatment of clinical inflammatory pain.

Intrathecal Bolus Administration of siRNAs Against Nav1.8 without Transfection Reagent Alleviates Inflammatory Pain

The effect of siRNAs against Nav1.8, formulated in phosphate buffered saline (PBS), on complete Freund’s adjuvant (CFA)-induced tactile hypersensitivity was evaluated in rats (FIG. 6). Of 3 Nav1.8 siRNAs tested, 2 siRNAs were efficacious against CFA-induced tactile hypersensitivity; AL-DP-4461, an unmodified siRNA with different chemical modifications but the same sequence as AL-DP-6050, and AL-DP-4459, a cholesterol-conjugated siRNA with the same chemical modifications and sequence as AL-DP-6050. With the dosing paradigms evaluated in this experiment, AL-DP-6980 (cholesterol-conjugated siRNA with the same chemical modifications and sequence as AL-DP-6050) was not efficacious against CFA-induced tactile hypersensitivity. The sequences of AL-DP-4461, AL-DP-4459 and AL-DP-6980 are shown in Table 6.

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ders, including chronic pain. Furthermore, these results demonstrate that siRNAs targeting Nav1.8, either with or without cholesterol-conjugation, formulated in saline and administered intrathecally by bolus injection, alleviate CFA-induced tactile hyperalgesia, and therefore represent a novel approach to providing effective treatment of clinical inflammatory pain.

The effect of siRNAs against Nav1.8, formulated in phosphate buffered saline (PBS), on complete Freund’s adjuvant (CFA)-induced tactile hypersensitivity was evaluated in rats after intrathecal pump infusion (FIG. 7, left) or intrathecal BID bolus injection (FIG. 7, right). Of 3 Nav1.8 siRNAs tested by continuous intrathecal pump infusion at 0.4 mg/day, 1 siRNA (AL-DP-6050, Table 1) was modestly efficacious against CFA-induced tactile hypersensitivity. AL-DP-6050, when tested by intrathecal BID bolus injection at 0.5 mg/bo-

lus, was efficacious against CFA-induced tactile hypersensi-
tivity.

For evaluating effects of siRNAs against Nav1.8 with continuous intrathecal pump infusion, adult male Sprague-Dawley rats received an injection of CFA into the hindpaw on day 0. Four groups of rats (with 5 rats per group) were treated starting on day 1 after CFA injection with either siRNA against Nav1.8 (AL-DP-6050, AL-DP-6218, or AL-DP-6219), or PBS. In all rats, test articles were intratheca-

lly administered by continuous osmotic mini-pump infusion with an infusion rate of 0.5 µl/hour, beginning on day 1. siRNAs were infused at 0.4 µg/day. Tactile hypersensitivity was measured as above, both before CFA injection to assess baseline thresholds, and then on day 4 after CFA and treatment with test articles (FIG. 7, left). In rats treated with PBS, tactile hypersensitivity was pronounced on day 4, as evidenced by reduced paw withdrawal threshold, as expected. In rats treated with AL-DP-6050 by continuous intrathecal pump infusion (0.4 µg/day), tactile thresholds were modestly normalized on day 4, demonstrating that the Nav1.8 siRNA, AL-DP-6050, is modestly efficacious with this dosing paradigm in vivo against inflammatory pain.

For evaluating effects of siRNAs against Nav1.8 with BID intrathecal bolus injection, adult male Sprague-Dawley rats received an injection of CFA into the hindpaw on day 0. Two groups of rats (with 4 to 5 rats per group) were treated starting on day 1 after CFA injection with either siRNA against Nav1.8 (AL-DP-6050, 0.5 mg/bolus) or PBS. Tactile hypersensitivity was assessed as described above. Tactile thresholds were measured before CFA injection to assess baseline thresholds, and then on day 4 after CFA injection and treatment with test articles (FIG. 7, right). As expected, in rats treated with PBS, tactile hypersensitivity was pronounced on day 4, as evidenced by reduced paw withdrawal threshold. In rats treated with AL-DP-6050 by BID intrathecal bolus injection (0.5 mg/bolus), tactile thresholds were substantially normalized on day 4, demonstrating that the Nav1.8 siRNA, AL-DP-6050, is modestly efficacious with this dosing paradigm in vivo against inflammatory pain.

These results further demonstrate that siRNAs targeting Nav1.8 without cholesterol-conjugation, formulated in saline and administered intrathecally by either bolus injection or continuous pump infusion, alleviate CFA-induced tactile hyperalgesia, and therefore represent a novel approach to providing effective treatment of clinical inflammatory pain.

The effect of siRNAs against Nav1.8, formulated in phosphate buffered saline (PBS), on complete Freund’s adjuvant (CFA)-induced thermal hypersensitivity was evaluated in rats (FIG. 8). Both unconjugated dsRNA AL-DP-6050 (Table 1) and cholesterol-conjugated dsRNA AL-DP-4459 (Table 6) were efficacious against CFA-induced thermal hypersensitivity with the BID bolus intrathecal dosing paradigm evaluated.

Adult male Sprague-Dawley rats received an injection of CFA into the hindpaw on day 0. Three groups of rats (with 4 to 5 rats per group) were treated starting on day 1 after CFA injection with either siRNA against Nav1.8 (AL-DP-6050 or AL-DP-4459), or PBS. In all rats, test articles were administered intrathecally by BID bolus injection (10 µl per bolus) beginning on day 1. AL-DP-4459 was dosed at 0.15 mg/bolus whereas AL-DP-6050 was dosed at 0.5 mg/bolus. Thermal hypersensitivity was measured by assessing paw withdrawal latency to a noxious thermal stimulus as described by Hargreaves and colleagues (Hargreaves, K., R. Dubner, et al. (1988) “A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia” Pain 32:77-88). Latency to withdrawal of a hindpaw in response to noxious radiant heat was determined. A maximal cut-off of 40 sec prevented tissue damage.

Thermal responses were measured before CFA injection to assess baseline thresholds, and then on day 4 after CFA injection and treatment with test articles. As expected, in rats treated with PBS, thermal hypersensitivity was pronounced on day 4, as evidenced by reduced paw withdrawal latency. In rats treated with AL-DP-6050 (0.5 mg/bolus) or AL-DP-4459 (0.15 mg/bolus) by intrathecal BID bolus injection, thermal latencies were normalized on day 4, demonstrating that the unconjugated Nav1.8 siRNA, AL-DP-6050, and the cholesterol-conjugated Nav1.8 siRNA AL-DP-4459 are efficacious with this dosing paradigm in vivo against inflammatory pain.

These results demonstrate that siRNAs targeting Nav1.8, either with or without cholesterol-conjugation, formulated in saline and administered intrathecally by bolus injection, alleviate CFA-induced thermal hyperalgesia, in addition to tactile hyperalgesia (above), and therefore represent a novel approach to providing effective treatment of multiple types of hyperalgesia in clinical inflammatory pain.

Intrathecal Bolus Administration of Cholesterol-Conjugated siRNA Against Nav1.8 without Transfection Reagent Alleviates Neuropathic Pain

The effect of AL-DP-4459 (Table 6) against Nav1.8, formulated in phosphate buffered saline (PBS), on spinal nerve ligation (SNL)-induced tactile and thermal hypersensitivity was evaluated in rats (FIG. 9). With the bolus intrathecal dosing paradigm evaluated (0.15 mg/bolus, BID), AL-DP-4459 was efficacious against SNL-induced tactile and thermal hypersensitivity.

Adult male Sprague-Dawley rats received unilateral ligation of the L5 and L6 spinal nerves on day 0 (SNL surgery). Three groups of rats (with 6 to 8 rats per group) were treated starting on day 3 after SNL surgery by intrathecal administration of either the siRNA AL-DP-4459 against
Nav1.8, or PBS. In 2 of these groups, AL-DP-4459 or PBS was administered by intrathecal bolus injections (5 μL per injection) to the lumbar level of the spinal cord twice per day (BID) on post-SNL days 3 through 7. In one group of rats, AL-DP-4459 was intrathecally administered by continuous osmotic mini-pump infusion at 0.18 mg/day, with an infusion rate of 0.5 μL/hour, on post-SNL days 3 through 7. Tactile and thermal hypersensitivities were assessed as described above. 

[0262] Tactile (FIG. 9, left) and thermal (FIG. 9, right) responses were measured before SNL surgery to assess baseline responses (BL), and on post-SNL day 3 before treatment with test articles to verify that tactile and thermal hyperalgesia had developed fully. In rats treated with PBS, tactile and thermal hypersensitivities were pronounced, as expected, on post-SNL days 3, 5 and 7 as evidenced by reduced paw withdrawal thresholds and reduced thermal latencies, respectively. The Nav1.8 siRNA AL-DP-4459, when intrathecally administered by continuous pump infusion at 0.18 mg/day, did not affect tactile or hypersensitivity significantly over the time-frame shown. In contrast, in rats treated with AL-DP-4459 by bolus BID (0.15 mg/bolus), tactile thresholds and thermal latencies were substantially normalized on post-SNL day 7 (day 5 of treatment), demonstrating that the Nav1.8 siRNA, AL-DP-4459, is efficacious in vivo against SNL-induced tactile and thermal hyperalgesia.

[0263] These results demonstrate that intrathecally administered cholesterol-conjugated siRNAs targeting Nav1.8, formulated in saline, are efficacious against experimental nerve injury-induced chronic pain in rats, and therefore, represent a novel approach to providing effective treatment of clinical neuropathic pain.

[0264] Unconjugated and Cholesterol-Conjugated siRNAs Targeting Nav1.8 are Stable in Human Cerebrospinal Fluid at 37°C.

[0265] To determine the stability in human cerebrospinal fluid (CSF) of unconjugated and cholesterol-conjugated siRNAs targeting Nav1.8, siRNA duplexes were incubated in human CSF for 48 hours at 37°C, and the single strands were measured by quantitative ion exchange chromatography. In this example, unconjugated siRNAs AL-DP-6050, AL-DP-6209, AL-DP-6217, AL-DP-6218 and AL-DP-6219 (Table 1), and cholesterol-conjugated siRNA AL-DP-4459 (Table 6) were evaluated. 30 μL of human CSF was mixed with 30 μL of 50 μM siRNA (150 pmol/well) in a 96-well plate, sealed to avoid evaporation, and incubated for 1 to 48 hours at 37°C. Incubation in 30 μL PBS for 48 hours at 37°C served as a control for nonspecific degradation. Reactions were stopped by the addition of 4 μL Proteinase K (20 mg/ml) and 25 μL of Proteinase K buffer, and incubation of this mixture for 20 min at 42°C. Samples were spin filtered through a 0.2 μm 96-well filter plate at 3000 rpm for 20 min. Incubation wells were washed with 50 μL Millipore water twice and the combined washing solutions were spin filtered also. A 5 μl aliquot of 50 μM 40-mer RNA was added to each sample to act as an internal standard (IS) for normalization of volume changes in the filtration volume. Samples were analyzed by ion exchange HPLC under denaturing conditions.

[0266] 1. HPLC System for analysis of cholesterol-conjugated siRNA AL-DP-4459

| Column: | Dionex DNAPac PA200 (4 × 250 mm analytical column) |
| Temp.: | 80°C. (denaturing conditions) |
| Flow: | 1 ml/min |
| Injection: | 50 μl |

Gradient Table:

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Gradient Table:

| Column: | Dionex DNAPac PA200 (4 × 250 mm analytical column) |
| Temp.: | 30°C. (denaturing conditions by pH = 11) |
| Flow: | 1 ml/min |
| Injection: | 50 μl |
| Detection: | 260 nm (reference wavelength 600 nm) |

| HPLC Eluent A: | 20 mM Na2PO4 in 10% ACN; pH = 11 |
| HPLC Eluent B: | 1M NaBr in A |

Gradient Table:

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Under the denaturing IEX-HPLC conditions, the duplexes eluted as two separated single strands. The internal standard eluted at higher retention times than the single strands of the duplex, and did not interfere with the analysis.

[0271] For every injection, the chromatograms were integrated automatically by the Dionex Chromeleon 6.60 HPLC software, but were adjusted manually as necessary. All peak areas were corrected by the following equation to the internal standard (IS) peak:

\[
\text{C}_{\text{IS}}(t) = \frac{\text{C}_{\text{IS}}(t)}{\text{C}_{\text{IS}}(t)} - \frac{\text{C}_{\text{IS}}(t)}{\text{C}_{\text{IS}}(t)}
\]

[0272] The % values for the remaining intact FLP at all time points are calculated by the following equation:

\[
\%\text{FLP}_{\text{remaining}} = \left( \frac{\text{C}_{\text{IS}}(t)}{\text{C}_{\text{IS}}(t)} \right) \times 100\%
\]

[0273] All values were normalized to the incubation at t=0 min.

[0274] The results for the unconjugated siRNAs are shown in FIG. 10. After 48 hours incubation at 37°C in PBS (PBS-}
all five siRNAs were completely stable, with no loss detectable. After 48 hours incubation at 37°C in human CSF, three (AL-DP-6050, AL-DP-6209 and AL-DP-6217) of the five siRNAs exhibited less than 20% loss, whereas two (AL-DP-6218 and AL-DP-6219) of the siRNAs exhibited greater than 50% loss. The results for the cholesterol-conjugated siRNA AL-DP-4459 are shown in FIG. 11. After 48 hours incubation at 37°C in PBS (PBS-48), AL-DP-4459 was completely stable, with no loss detectable. When assessed for stability in human CSF, AL-DP-4459 was found to be stable at 37°C for 48 hours, with less than 20% variation detected over this time period.

[0275] Unconjugated and Cholesterol-Conjugated siRNAs Targeting Nav1.8 Reduce Nav1.8 mRNA in a Dose-Dependent Manner in Primary Rat Sensory Neuronal Cultures

[0276] Another effective siRNA (AL-DP-6050, Table 1) against Nav1.8 from the single dose screen in primary cultures of rat dorsal root ganglion cells and its cholesterol conjugate AL-DP-4459 (Table 6) were further characterized for dose dependence. For the dose response curves, transfections were performed using Lipofectamine 2000 (see below) with the following concentrations of siRNA: 200, 80, 32, 12.8, 5.12, 2.5, 1.25, and 0.625 nM (FIG. 12).

[0277] DRG neurons were transfected 24 h post-plating. For each well, 0.4 μL Lipofectamine™ 2000 (Invitrogen Corporation, Carlsbad, Calif.) was used and transfections were performed according to the manufacturer’s protocol. Specifically, the siRNA: Lipofectamine™ 2000 complexes were prepared as follows. The appropriate amount of siRNA was diluted in Opti-MEM 1 Reduced Serum Medium and mixed gently. The Lipofectamine™ 2000 was vortexed before use; then for each well of a 96 well plate, 0.4 μL Lipofectamine™ 2000 was diluted in 25 μL of Opti-MEM 1 Reduced Serum Medium, mixed gently and incubated for 5 minutes at room temperature. After the 5 minute incubation, 1 μL of the diluted siRNA was combined with the diluted Lipofectamine™ 2000 (total volume, 26.4 μL). The complex was mixed gently and incubated for 20 minutes at room temperature to allow the siRNA: Lipofectamine™ 2000 complexes to form. Then 100 μL of serum-free F12-HAM’s Medium containing glutamine (Invitrogen Gibco, Carlsbad Calif., USA) supplemented with 50 μg/ml NFG 2.5S (Promega Corp., Madison Wis., USA) and 1:50 B27 supplement (Invitrogen Gibco, Carlsbad Calif., USA) was added to the transfection complexes, and mixing was achieved by gently pipetting up and down. The growth medium was removed from the DRG cells and 100 μL of the above transfection complex mixture was added to each well of a 96-well plate. After 20 h of incubation at 37°C, 5% CO2 in a humidified incubator, supernatant was removed from the cells, fresh F12-HAM’s medium containing glutamine supplemented with 5% FBS, 5% horse serum (both Invitrogen Gibco, Carlsbad Calif., USA), 50 ng/ml mouse NFG 2.5S (Promega Corp., Madison Wis., USA) and 1:100 Penicillin/Streptomycin (Invitrogen Gibco, Carlsbad Calif., USA) was added. The cells were incubated for another 20-24 h at 37°C, 5% CO2 in a humidified incubator, and Nav1.8 mRNA was quantified by the qDNA assay, as described previously.

[0278] FIG. 12 provides the result for the selected siRNA AL-DP-6050 and its cholesterol conjugate AL-DP-4459 from a dose response experiment. AL-DP-6050 and its cholesterol conjugate AL-DP-4459 inhibited Nav1.8 mRNA expression relative to alpha-synuclein (SNCA) in a dose-dependent manner, with maximal inhibitions of ~40% at >50 nM siRNA, in this experiment.

[0279] Intrathecal Bolus Administration of Unconjugated siRNA Against Nav1.8 without Transfection Reagent Alleviates Neuropathic Pain

[0280] The effect of AL-DP-6050 (Table 1) against Nav1.8, formulated in phosphate buffered saline (PBS), on spinal nerve ligation (SNL)-induced thermal hypersensitivity was evaluated in rats (FIG. 13). With the bolus intrathecal dosing paradigm evaluated (0.15 mg/bolus, BID), AL-DP-6050 was efficacious against SNL-induced thermal hypersensitivity.

[0281] Adult male Sprague-Dawley rats received unilateral ligation of the L5 and L6 spinal nerves on day 0 (SNL surgery). Two groups of rats (with 8 rats per group) were treated starting on day 3 after SNL surgery by intrathecal bolus injection with either the siRNA AL-DP-6050 against Nav1.8, or PBS. Intrathecal bolus injections (0.15 mg in 5 μL per injection) were administered to the lumbar level of the spinal cord twice per day (BID) on post-SNL days 3 through 7. Thermal hypersensitivity was assessed as described above.

[0282] Thermal responses were measured before SNL surgery to assess baseline responses (BL), and on post-SNL day 3 before treatment with test articles to verify that thermal hyperalgesia had developed fully. In rats treated with PBS, thermal hypersensitivity was pronounced, as expected, on post-SNL days 3, 5 and 7 as evidenced by reduced thermal latencies. In contrast, in rats treated with AL-DP-6050 by bolus BID (0.15 mg/bolus), thermal latencies were substantially normalized on post-SNL days 5 (day 3 of treatment) and 7 (day 5 of treatment), demonstrating that the Nav1.8 siRNA, AL-DP-6050, is efficacious in vivo against SNL-induced thermal hyperalgesia.

[0283] These results demonstrate that siRNAs targeting Nav1.8, formulated in saline and administered by intrathecal bolus injection, are efficacious against experimental nerve injury-induced chronic pain in rats, and therefore, represent a novel approach to providing effective treatment of clinical neuropathic pain.

[0284] Intrathecal Bolus Administration of ND98-2.7 Liposomal Formulation of siRNA Against Nav1.8 Alleviates Neuropathic Pain

[0285] The effect of AL-DP-6050 (Table 1) against Nav1.8, formulated in ND98-2.7 (described below), and administered by intrathecal bolus injection, on spinal nerve ligation (SNL)-induced thermal hypersensitivity was evaluated in rats (FIG. 14). With the bolus intrathecal dosing paradigm evaluated (5 micrograms/bolus, daily), AL-DP-6050 was efficacious against SNL-induced thermal hyperalgesia.

[0286] Adult male Sprague-Dawley rats received unilateral ligation of the L5 and L6 spinal nerves on day 0 (SNL surgery). Two groups of rats (with 6 rats per group) were treated starting on day 3 after SNL surgery by intrathecal bolus injection with either the siRNA AL-DP-6050 against Nav1.8, formulated in ND98-2.7, or PBS. Intrathecal bolus injections (5 micrograms in 5 μL per injection) were administered to the lumbar level of the spinal cord daily on post-SNL days 3 through 5. Thermal hypersensitivity was assessed as described above.

[0287] Thermal responses were measured before SNL surgery to assess baseline responses (BL), and on post-SNL day 3 before treatment with test articles to verify that thermal hyperalgesia had developed fully. In rats treated with PBS, thermal hypersensitivity was pronounced, as expected, on post-SNL days 3, 5, 7 and 10 as evidenced by reduced thermal latencies. In contrast, in rats treated with AL-DP-6050 formulated in ND98-2.7 liposomes, by intrathecal bolus daily
injection (5 micrograms/bolus), thermal latencies were substantially normalized on post-SNL day 5 (day 3 of treatment), demonstrating that the Nav1.8 siRNA, AL-DP-6050, formulated in ND98-2.7 liposomes and administered by intrathecal injection, is efficacious in vivo against SNL-induced thermal hyperalgesia. Moreover, the dose level of siRNA required for efficacy with the ND98-2.7 liposomal formulation (5 micrograms per day) was much lower than that observed for efficacy with the PBS formulation (300 micrograms per day).

These results demonstrate that siRNAs targeting Nav1.8, administered by intrathecal bolus injection and formulated in ND98-2.7 liposomes, are efficacious against experimental nerve injury-induced chronic pain in rats, and therefore, represent a novel approach to providing effective treatment of clinical neuropathic pain.

Intravenous Bolus and Continuous Pump Administration of ND98-2.7 Liposomal Formulation of siRNA Against Nav1.8 Alleviates Neuropathic Pain

The effect of AL-DP-6050 (Table 1) against Nav1.8, formulated in ND98-2.7, and administered by intravenous bolus injection or intravenous continuous pump infusion, on spinal nerve ligation (SNL)-induced thermal hyperalgesia was evaluated in rats (FIG. 14). With the bolus intravenous dosing paradigm evaluated (daily 0.5 mg/kg bolus, equivalent to approximately 2 mg/kg/bolus), and with the continuous intravenous pump paradigm evaluated (0.24 mg/day, equivalent to approximately 1 mg/kg/day), AL-DP-6050, formulated in ND98-2.7 liposomes, was efficacious against SNL-induced thermal hyperalgesia.

Adult male Sprague-Dawley rats received unilateral ligation of the L5 and L6 spinal nerves on day 0 (SNL surgery). Two groups of rats (with 6 rats per group) were treated starting on day 3 after SNL surgery by intravenous bolus injection or intravenous continuous pump infusion with the siRNA AL-DP-6050 against Nav1.8, formulated in ND98-2.7. Intravenous bolus injections (0.5 mg in 1 mL per bolus) were administered daily on post-SNL days 3 through 5. Intravenous continuous pump infusion (10 μL/hour, equivalent to 0.24 mg/day) was administered on post-SNL days 3 through 10 via a cannula in the jugular vein. Thermal hyperalgesia was assessed as described above.

Thermal responses were measured before SNL surgery to assess baseline responses (BL), and on post-SNL day 3 before treatment with test articles to verify that thermal hyperalgesia had developed fully. Thermal hyperalgesia was pronounced, as expected, on post-SNL day 3, before treatment, as evidenced by reduced paw withdrawal latencies. In contrast, in rats treated with AL-DP-6050 formulated in ND98-2.7 liposomes, by intravenous bolus daily injection (0.5 mg/bolus), thermal latencies were substantially normalized on post-SNL day 5 (day 3 of treatment), and post-SNL day 7 (2 days after the last intravenous bolus treatment) demonstrating that the Nav1.8 siRNA, AL-DP-6050, formulated in ND98-2.7 liposomes and administered by intravenous bolus injection, is efficacious in vivo against SNL-induced thermal hyperalgesia. Furthermore, in rats treated with AL-DP-6050 formulated in ND98-2.7 liposomes, by intravenous continuous pump infusion (0.24 mg/day), thermal latencies were substantially normalized on post-SNL days 5 (day 3 of treatment), 7 (day 5 of treatment) and 10 (day 8 of treatment).

These results demonstrate that siRNAs targeting Nav1.8, formulated in ND98-2.7 liposomes, and administered by intravenous bolus injection or intravenous continuous pump infusion, are efficacious against experimental nerve injury-induced chronic pain in rats, and therefore, represent a novel approach to providing effective treatment of clinical neuropathic pain. Moreover, these results demonstrate that ND98-2.7 liposomal formulation of siRNA can provide effective delivery of siRNA to sensory neurons of the dorsal root ganglion, with systemic administration.

Formulation Procedure

The lipoidol ND98-4HCl (MW 1487), Cholesterol (Sigma-Aldrich), and PEG-Ceramide C16 (Avanti Polar Lipids) were used to prepare lipid-siRNA nanoparticles.

Stock solutions of each in ethanol were prepared: ND98 (FI 15, ND98 Isomer I), 133 mg/mL; Cholesterol, 25 mg/mL; PEG-Ceramide C16, 100 mg/mL. ND98, Cholesterol, and PEG-Ceramide C16 stock solutions were then combined in a 42:48:10 molar ratio. Combined lipid solution was mixed rapidly with aqueous siRNA (in sodium acetate pH 5) such that the final ethanol concentration was 55-45% and the final sodium acetate concentration was 100-300 mM. Lipid-siRNA nanoparticles formed spontaneously upon mixing. Depending on the desired particle size distribution, the resultant nanoparticle mixture was in some cases extruded through a polycarbonate membrane (100 nm cut-off) using a thermostable extruder (Lipex Extruder, Northern Lipids, Inc). In other cases, the extrusion step was omitted. Ethanol removal and simultaneous buffer exchange was accomplished by either dialysis or tangential flow filtration. Buffer was exchanged to phosphate buffered saline (PBS) pH 7.2.

Characterization of Formulations

Formulations prepared by either the standard or extrusion-free method are characterized in a similar manner. Formulations are first characterized by visual inspection. They should be whitish translucent solutions free from aggregates or sediment. Particle size and particle size distribution of lipid-nanoparticles are measured by dynamic light scattering using a Malvern Zetasizer Nano ZS (Malvern, USA). Particles should be 20-300 nm, and ideally, 40-100 nm in size. The particle size distribution should be unimodal. The total siRNA concentration in the formulation, as well as the entrapped fraction, is estimated using a dye exclusion assay. A sample of the formulated siRNA is incubated with the RNA-binding dye Ribogreen (Molecular Probes) in the presence or absence of a formulation disrupting surfactant, 0.5% Triton-X100. The total siRNA in the formulation is determined by the signal from the sample containing the surfactant, relative to a standard curve. The entrapped fraction is determined by subtracting the “free” siRNA content (as measured by the signal in the absence of surfactant) from the total siRNA content. Percent entrapped siRNA is typically >85%.

dsRNA Expression Vectors

In another aspect of the invention, Nav1.8 specific dsRNA molecules that modulate Nav1.8 gene expression activity are expressed from transcription units inserted into DNA or RNA vectors (see, e.g., Couture, A. et al., **JIG** (1996), 12:5-10; Skillem, A., et al., International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Pat. No. 6,054, 299). These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be incorporated and inherited as a transgene integrated into the host genome. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Trasmann, et al., **Proc. Natl. Acad. Sci. USA** (1995) 92:1292).
The individual strands of a dsRNA can be transcribed by promoters on two separate expression vectors and co-transfected into a target cell. Alternatively, each individual strand of the dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In a preferred embodiment, a dsRNA is expressed as an inverted repeat joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.


The promoter driving dsRNA expression in either a DNA plasmid or viral vector of the invention may be a eukaryotic RNA polymerase I (e.g. ribosomal RNA promoter), RNA polymerase II (e.g. CMV early promoter or actin promoter or U1 snRNA promoter) or preferably RNA polymerase III promoter (e.g. U6 snRNA or 7SK RNA promoter) or a prokaryotic promoter, for example the T7 promoter, provided the expression plasmid also encodes T7 RNA polymerase required for transcription from a T7 promoter. The promoter can also direct transgene expression to the pancreas (see, e.g. the insulin regulatory sequence for pancreas (Bucchini et al., 1986, Proc. Natl. Acad. Sci. USA 83:2511-2515)).

In addition, expression of the transgene can be precisely regulated, for example, by using an inducible regulatory sequence and expression systems such as a regulatory sequence that is sensitive to certain physiological regulators, e.g., circulating glucose levels, or hormones (Docherty et al., 1994, FASEB J. 8:20-24). Such inducible expression systems, suitable for the control of transgene expression in cells or in mammals include regulation by edecysone, by estrogen, progesterone, tetracycline, chemical inducers of dimeterization, and isopropyl-beta-D-thiogalactopyranoside (EPTG). A person skilled in the art would be able to choose the appropriate regulatory/promoter sequence based on the intended use of the dsRNA transgene.

Preferably, recombinant vectors capable of expressing dsRNA molecules are delivered as described below, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of dsRNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the dsRNAs bind to target RNA and modulate its function or expression. Delivery of dsRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells explanted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

dsRNA expression DNA plasmids are typically transfected into target cells as a complex with cationic lipid carriers (e.g. Oligofectamine) or non-cationic lipid-based carriers (e.g. Transit-TKOTM). Multiple lipid transflections for dsRNA-mediated knockdowns targeting different regions of a single Nav1.8 gene or multiple Nav1.8 genes over a period of a week or more are also contemplated by the invention. Successful introduction of the vectors of the invention into host cells can be monitored using various known methods. For example, transient transfection, can be signaled with a reporter, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Stable transfection of ex vivo cells can be ensured using markers that provide the transfected cells with resistance to specific environmental factors (e.g., antibiotics and drugs), such as hygromycin B resistance.

The Nav1.8 specific dsRNA molecules can also be inserted into vectors and used as gene therapy vectors for human patients. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Pat. No. 5,328,470) or by stereotactic injection (see e.g., Chen et al. (1994) Proc. Natl. Acad. Sci. USA 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.
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gacaaccgg auuuauacut 21

<210> SEQ ID NO 6
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 6

aguuaaacuc cggguguacut 21

<210> SEQ ID NO 7
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<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (13) (13)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (15) (15)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<400> SEQUENCE: 7

cuuuacaco aggcaggtct 21

<210> SEQ ID NO 8
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

FEATURE:
NAME/KEY: modified_base
LOCATION: (15) (15)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 8
uccucgguug uuguuuacgt
21

SEQ ID NO 9
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
NAME/KEY: modified_base
LOCATION: (3) (5)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (9) (12)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (15) (15)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (16) (16)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (18) (18)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

SEQUENCE: 9
aaccggauuu uuaacucat
21

SEQ ID NO 10
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
NAME/KEY: modified_base
LOCATION: (3) (3)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (7) (7)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 10
uguauuauu uaccggguu
21

SEQ ID NO 11
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

FEATURE:

NAME/KEY: modified_base
LOCATION: (1) (1)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (3) (3)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (5) (5)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (7) (7)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (10) (12)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (16) (16)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (17) (17)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (18) (18)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (19) (19)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 11

ugacgacucgcacagt 21

SEQ ID NO: 12
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:

NAME/KEY: modified_base
LOCATION: (2) (2)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (12) (12)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (16) (16)

OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (18) (18)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:

NAME/KEY: modified_base
LOCATION: (19) (19)

OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 12

ucaguugggucaugucacagt 21

SEQ ID NO: 13
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
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**FEATURE:**

**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

**FEATURE:**

**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (2)...(2)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (5)...(6)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (9)...(9)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (11)...(11)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (16)...(16)

**OTHER INFORMATION:** 2'-O-methyluridine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (18)...(18)

**OTHER INFORMATION:** 2'-O-methyluridine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (19)...(19)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (3)...(3)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (2)...(4)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**SEQUENCE:** 13

acaccagcg caggauagt t 21

**SEQ ID NO:** 14

**LENGTH:** 21

**TYPE:** DNA

**ORGANISM:** Artificial Sequence

**FEATURE:**

**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

**FEATURE:**

**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (3)...(3)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (19)...(19)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (2)...(4)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base

**SEQUENCE:** 14

gacacccagc gccggauagt t 21

**SEQ ID NO:** 15

**LENGTH:** 21

**TYPE:** DNA

**ORGANISM:** Artificial Sequence

**FEATURE:**

**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

**FEATURE:**

**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**FEATURE:**

**NAME/KEY:** modified base

**LOCATION:** (2)...(4)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified base
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14) (14)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15) (15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (17) (17)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 15

acccggauuu uacuaacact t

<210> SEQ ID NO 16
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 16

guguaguanas aaccgggguu t

<210> SEQ ID NO 17
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (3) (3)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
caggcaugga accaauagct 21

<210> SEQ ID NO 18
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (2) (3)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (3) (3)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13) (13)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<210> SEQ ID NO 19
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (2) (3)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5) (5)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) (9)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
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<222> LOCATION: (12) (12)
<223> OTHER INFORMATION: 2'-0-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14) (14)
<223> OTHER INFORMATION: 2'-0-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: 2'-0-methyluridine-5'-phosphate

<400> SEQUENCE: 19

cuuaacacca gcgcaggaat t

<210> SEQ ID NO 20
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (3)
<223> OTHER INFORMATION: 2'-0-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: 2'-0-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (3)
<223> OTHER INFORMATION: 2'-0-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7) (7)
<223> OTHER INFORMATION: 2'-0-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9) (9)
<223> OTHER INFORMATION: 2'-0-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) (12)
<223> OTHER INFORMATION: 2'-0-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) (15)
<223> OTHER INFORMATION: 2'-0-methylcytidine-5'-phosphate

<400> SEQUENCE: 21

auccugcgu gguguaaagt t
uuuaacacua cccgcuuugg t

caaaacgggu uauguuaaat t

guggugcaug cccgaacug t
cagucgggu caugcaacact

cggauuuua cuacaccaagt
FEATURE: <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

NAME/KEY: modified base
LOCATION: (7) (7)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

NAME/KEY: modified base
LOCATION: (11) (11)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 26

cugguguag uaaaaucogt t 21

SEQ ID NO 27
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
NAME/KEY: modified base
LOCATION: (1) (1)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (3) (3)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (6) (7)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (10) (10)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (12) (12)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (16) (17)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (19) (19)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 27

uacacacgac gcggaugut t 21

SEQ ID NO 28
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
NAME/KEY: modified base
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<221> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<222> LOCATION: (18) (18)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 28

acaccccug cugguuguat t

<210> SEQ ID NO 29
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 29

ggucucug ccaccagcu t
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (3)..<3)..<3)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..<10)..<10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12)..<12)..<12)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 30
accaauggcc acagagaacct t

<210> SEQ ID NO 31
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<222> LOCATION: (1)..<1)..<1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..<7)..<7)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9)..<9)..<9)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..<10)..<10)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12)..<12)..<12)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15)..<15)..<15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19)..<19)..<19)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 31
cccauguucu auggagacct t

<210> SEQ ID NO 32
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
2'-O-methylcytidine-5'-phosphate

2'-O-methyluridine-5'-phosphate

Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

Description of Artificial Sequence: Synthetic oligonucleotide

SEQ ID NO 33
LENGTH: 31
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

FEATURE:
NAME/KEY: modified_base
LOCATION: (1), (1)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (5), (6)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (9), (9)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (7), (7)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (8), (8)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (10), (10)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (13), (13)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (17), (17)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (18), (18)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (19), (19)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified_base
LOCATION: (21)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQ ID NO 34
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9) (9)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 34

gagcucca agoaacoagt
<210> SEQ ID NO 35
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (2) (2)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (7) (7)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
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<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (13) (14)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) (18)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<400> SEQUENCE: 35
cuacogaca caacggacat
<210> SEQ ID NO 36
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
ugucggu gugcguagt t

aagucauaug guagcuacct t

<210> SEQ ID NO 37
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) . (5)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6) . (6)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7) . (7)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) . (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9) . (9)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10) . (10)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) . (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12) . (12)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13) . (13)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14) . (14)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15) . (15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) . (16)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (17) . (17)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (18) . (18)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (10) ... (10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12) ... (12)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 38

gagaucaaccauagacuut

<210> SEQ ID NO 39
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) ... (4)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6) ... (6)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7) ... (7)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) ... (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12) ... (12)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) ... (17)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (18) ... (18)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<400> SEQUENCE: 39

uuugaucuaaugaucaucat

<210> SEQ ID NO 40
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7) ... (7)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) ... (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
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<222> LOCATION: (15) (15)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 40

ugaacucau uagacaaat t

<210> SEQ ID NO 41
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<221> ID: modified_base
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (1) (2)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (3) (3)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (5) (5)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (7) (7)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
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<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
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<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (11) (12)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (13) (14)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
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<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<220> FEATURE:
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<220> FEATURE:
<221> ID: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 41
cucucucacug uccgcucuct t
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

NAME/KEY: modified base
LOCATION: (10) (10)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

SEQUENCE: 42

 gaggggaac agusagagst t

SEQ ID NO 43
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

NAME/KEY: modified base
LOCATION: (3) (4)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (7) (8)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (9) (9)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (10) (12)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (14) (14)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (17) (18)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

SEQUENCE: 43

aaccagugu uugggagcgt t

SEQ ID NO 44
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

NAME/KEY: modified base
LOCATION: (5) (5)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (7) (7)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

SEQUENCE: 44
cgccacaa gacugguut t

<210> SEQ ID NO 45
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (2) (2)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (3) (3)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5) (5)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6) (6)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7) (7)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9) (9)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10) (10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12) (12)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13) (13)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14) (14)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15) (15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) (16)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (17) (17)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (18) (18)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20) (20)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (21) (21)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 45

cucacuguc gcgccuauagt t
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: \textit{2'-O-methylcytidine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13) (13)
<223> OTHER INFORMATION: \textit{2'-O-methylcytidine-5'}-phosphate

<400> SEQUENCE: 46
caugagcgg asacugagst 21

<210> SEQ ID NO 47
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (2)
<223> OTHER INFORMATION: \textit{2'-O-methylcytidine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6) (7)
<223> OTHER INFORMATION: \textit{2'-O-methyluridine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) (8)
<223> OTHER INFORMATION: \textit{2'-O-methylcytidine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9) (9)
<223> OTHER INFORMATION: \textit{2'-O-methyluridine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) (11)
<223> OTHER INFORMATION: \textit{2'-O-methyluridine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14) (14)
<223> OTHER INFORMATION: \textit{2'-O-methyluridine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) (18)
<223> OTHER INFORMATION: \textit{2'-O-methylcytidine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: \textit{2'-O-methyluridine-5'}-phosphate

<400> SEQUENCE: 47
ccaaguccua uggagacgt 21

<210> SEQ ID NO 48
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5) (5)
<223> OTHER INFORMATION: \textit{2'-O-methylcytidine-5'}-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) - (8)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10) - (10)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 48
agcuccacau agacuccugst t

<210> SEQ ID NO: 49
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<210> SEQ ID NO: 50
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base

<400> SEQUENCE: 49
caguucuug ugcgucuut t
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**LOCATION:** (8) (8)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (10) (10)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**SEQUENCE:** 50

agacgggccac aaagacugt t

**SEQ ID NO:** 51

**LENGTH:** 21

**TYPE:** DNA

**ORGANISM:** Artificial Sequence

**FEATURE:**

**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

**FEATURE:**

**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (3) (3)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (4) (4)

**OTHER INFORMATION:** 2'-O-methyluridine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (7) (7)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (11) (11)

**OTHER INFORMATION:** 2'-O-methyluridine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (13) (13)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (15) (15)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**SEQUENCE:** 51

ggcugcgagg ugccagaagat t

**SEQ ID NO:** 52

**LENGTH:** 21

**TYPE:** DNA

**ORGANISM:** Artificial Sequence

**FEATURE:**

**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

**FEATURE:**

**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (8) (8)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**FEATURE:**

**NAME/KEY:** modified_base

**LOCATION:** (16) (16)

**OTHER INFORMATION:** 2'-O-methylcytidine-5'-phosphate

**SEQUENCE:** 52

cucuggcacugcaggctt t
<210> SEQ ID NO 53
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1), (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (2), (2)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (3), (4)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5), (5)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6), (6)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7), (7)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8), (8)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (9), (9)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10), (10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11), (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12), (12)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<400> SEQUENCE: 53

cucucucugag gcgscgcacgt t

<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12), (12)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<400> SEQUENCE: 54
cgucgucgcc ucagagaggt t

<210> SEQ ID NO 55
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

FEATURE: NAME/KEY: modified_base
LOCATION: (2) (2)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (3) (3)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (4) (5)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (6) (6)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (8) (8)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (9) (9)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (11) (11)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (12) (12)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (14) (14)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (16) (16)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE: NAME/KEY: modified_base
LOCATION: (18) (18)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 55
gucuucaguucuucuactt

SEQ ID NO 56
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
FEATURE:
NAME/KEY: modified_base
LOCATION: (3) (3)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
FEATURE:
NAME/KEY: modified_base
LOCATION: (10) (10)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

SEQUENCE: 56
uguuaaugccagugaagactt
<210> SEQ ID NO 57
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) (5)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (8) (8)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (10) (10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15) (15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) (17)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (18) (18)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 57
caacagcgc aggagcuucat

<210> SEQ ID NO 58
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 58
agacaucccg cguugguuguat
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

FEATURE:
NAME/KEY: modified base
LOCATION: (6) (6)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (8) (8)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (9) (9)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (10) (10)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (13) (13)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (14) (14)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (16) (16)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (18) (18)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

FEATURE:
NAME/KEY: modified base
LOCATION: (21) (21)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 59
agaagauuca guaucggtat

SEQ ID NO 60
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
FEATURE:
NAME/KEY: modified base
LOCATION: (4) (4)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
FEATURE:
NAME/KEY: modified base
LOCATION: (9) (9)
OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
FEATURE:
NAME/KEY: modified base
LOCATION: (13) (13)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
FEATURE:
NAME/KEY: modified base
LOCATION: (16) (16)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
FEATURE:
NAME/KEY: modified base
LOCATION: (21) (21)
OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

SEQUENCE: 60
uccagauuca guaucucutt
ucacagcac acacggact t

guccggugug uacguagat t

ucacagcac acacggact t

guccggugug uacguagat t
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<222> LOCATION: (5) (5)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (11) (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15) (15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16) (16)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) (19)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 63

agucauagg uagcucoct t

<210> SEQ ID NO 64
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) (8)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) (11)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13) (13)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 64

ggagcucauca uagcaacut t

<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1) (1)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
65

ucuagugga gcuucagcgt

21

66

gcuggagcu caccuagat
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<220> LOCATION: (3)...(4)
<220> FEATURE:
<221> NAME/KEY: modified base
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<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (13)...(14)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (16)...(16)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (17)...(17)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (18)...(19)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 67

agaucuuugu ggcggucuut

<210> SEQ ID NO 68
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate

<400> SEQUENCE: 68

aagaagccga caagagaacut
<222> LOCATION: (2) (2)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (4) (4)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (5) (5)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (7) (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (9) (10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (12) (13)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (16) (15)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified base
<222> LOCATION: (17) (17)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<400> SEQUENCE: 69
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<210> SEQ ID NO 70
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<200> SEQUENCE: 70
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<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (10) . (10)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11) . (11)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13) . (13)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (15) . (15)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19) . (19)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 71

gguuuuauac uacaccagct t

<210> SEQ ID NO: 72
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) . (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12) . (12)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 72
gcuggugug uussaaucct t

<210> SEQ ID NO: 73
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) . (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (12) . (12)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate

<400> SEQUENCE: 73
cgcugcugc gcgguuauct t

<210> SEQ ID NO: 74
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8) . (8)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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Other Information: Description of Artificial Sequence: Synthetic oligonucleotide

Sequence: 78

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Length: 21

Organism: Artificial Sequence

Synthetic oligonucleotide

Date: May 26, 2011
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 79
uguauuuag gucuauuact t

<210> SEQ ID NO 80
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 80
guaaugacgc uaaauuact t

<210> SEQ ID NO 81
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 81
cguuucgc guuauuact t

<210> SEQ ID NO 82
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 82
uggauacgc acgaagct t

<210> SEQ ID NO 83
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 83
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<210> SEQ ID NO 84
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 84

aguaaagca ccgaggucgt t

<210> SEQ ID NO 85
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 85

gucgcuuac uccggaguc t

<210> SEQ ID NO 86
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 86

gacuucggag uaaagcogat t

<210> SEQ ID NO 87
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 87

aauaguguca cgaccuugat t

<210> SEQ ID NO 88
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 88
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<210>  SEQ ID NO 89
<211>  LENGTH: 21
<212>  TYPE: DNA
<213>  ORGANISM: Artificial Sequence
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400>  SEQUENCE: 89
agacuugua coguaucut

<210>  SEQ ID NO 90
<211>  LENGTH: 21
<212>  TYPE: DNA
<213>  ORGANISM: Artificial Sequence
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400>  SEQUENCE: 90
acgauacgu agcagucut

<210>  SEQ ID NO 91
<211>  LENGTH: 21
<212>  TYPE: DNA
<213>  ORGANISM: Artificial Sequence
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400>  SEQUENCE: 91
aguuuaauuu uacggucut

<210>  SEQ ID NO 92
<211>  LENGTH: 21
<212>  TYPE: DNA
<213>  ORGANISM: Artificial Sequence
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400>  SEQUENCE: 92
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<210>  SEQ ID NO 93
<211>  LENGTH: 21
<212>  TYPE: DNA
<213>  ORGANISM: Artificial Sequence
<220>  FEATURE:
<223>  OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220>  FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 93

aaugaguc aaguagcugt t

<210> SEQ ID NO 94
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 94

cagguagogue accuauuu t

<210> SEQ ID NO 95
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 95

ugacacgca uacgaucat t

<210> SEQ ID NO 96
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 96

ugcaucauau ggcgaacat t

<210> SEQ ID NO 97
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 97

ucaaagcucc ugaaccouct t

<210> SEQ ID NO 98
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 98

gagguucgaagggcuuugat t 21

<210> SEQ ID NO 99
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 99

aggggccccu ucugauuu t 21

<210> SEQ ID NO 100
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 100

aaucgagaagagcccgct t 21

<210> SEQ ID NO 101
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 101

ccuugauccu uugucaauu t 21

<210> SEQ ID NO 102
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 102

aaucgacaaagguacacaggt t 21
<210> SEQ ID NO 103
<211> LENGTH: 21
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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gugguucuc ccauuggcat t

21

<210> SEQ ID NO 104
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<400> SEQUENCE: 104

ugcgaugga gagaaccaact t

21

<210> SEQ ID NO 105
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<400> SEQUENCE: 105

caaaaggcc aucgagagct t

21

<210> SEQ ID NO 106
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<400> SEQUENCE: 106

agcuucgau ggcuuuggt t

21

<210> SEQ ID NO 107
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<400> SEQUENCE: 107
aaagggccauau ccgagcuaaau t

<210> SEQ ID NO 108
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 108

auagcuuccga uagggccuunt t

<210> SEQ ID NO 109
<211> LENGTH: 21
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
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<400> SEQUENCE: 109

ggugcaucac cuuaccaucgt t

<210> SEQ ID NO 110
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 110

ucgguauaguc uagugccacct t

<210> SEQ ID NO 111
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 111

aacuacacuag acacaccaaat t

<210> SEQ ID NO 112
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 112

uucgguugua cggguaugut t

SEQ ID NO 113
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:

OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 113

uucgguuauc cggguagucat t

SEQ ID NO 114
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:

OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 114

ugacuccgga guaagcgcat t

SEQ ID NO 115
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:

OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 115

gaaacgccg gcguagucat t

SEQ ID NO 116
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:

OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:

OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 116

ugacuccgco gcguuuuct t

SEQ ID NO 117
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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accggaaaaa uacuccgct t

SEQ ID NO 119
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

-SEQUENCE: 117

21

gcggagauu uuuucggt t

SEQ ID NO 119
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

-SEQUENCE: 118

21

uuaucgcua auccacugt t

SEQ ID NO 120
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

-SEQUENCE: 119

21

cagcggauu agcgaagat t

SEQ ID NO 121
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

-SEQUENCE: 120

21

uccgccgcu uacuccggt t

SEQ ID NO 121
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE: OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

-SEQUENCE: 121

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uccggagaa aggcagagct t

21

gccuuacuc gcagucacut t

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acuagcuacc guacgugst t 21

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<400> SEQUENCE: 132

ccagaagc guaccaagt t 21

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<400> SEQUENCE: 134

cuacgcugug agacuauct t 21

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auaagcuaca cagcaagct t 21

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<400> SEQUENCE: 136

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<400> SEQUENCE: 138

cgaagggucu gaagggcuut t

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<400> SEQUENCE: 139

agcccuucaga acccuucgcct t

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<400> SEQUENCE: 143
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<400> SEQUENCE: 148

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<400> SEQUENCE: 149

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<400> SEQUENCE: 150

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<400> SEQUENCE: 151

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<400> SEQUENCE: 152

acggagaucu auuggcugu t

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<400> SEQUENCE: 154

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<212> TYPE: DNA
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FEATURES:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURES:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 155
cccaaaugg aucacuuu t
21

SEQ ID NO 156
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURES:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 156
aaaggugau cauugugg t
21

SEQ ID NO 157
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURES:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 157
ugcuuuucu aggcucgc t
21

SEQ ID NO 158
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURES:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 158
gcggagacua gaaagacat t
21

SEQ ID NO 159
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURES:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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**Sequence 160:**
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ugccgagac ugcacagct t
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**Sequence 161:**
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gucucgcua ucaugcagt t
```

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cugcaugaa ugcgcagact t
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ucaaaaauau ugcuuucag t
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ucgaggcau uguuugat t

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<400> SEQUENCE: 165

cocgugcca gaucaagat t

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<400> SEQUENCE: 167

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uguugguac gauggccaat t 21

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gcagguagc agcuccat t 21

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ucuuggagc gacccgat t 21

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gcuccuugaa ccucucgt t 21

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**FEATURE:**
**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**SEQUENCE:** 174

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**SEQ ID NO 175**
**LENGTH: 21**
**TYPE: DNA**
**ORGANISM: Artificial Sequence**
**FEATURE:**
**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
**FEATURE:**
**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**SEQUENCE:** 175

ugcgccgcu uccucgaat t

**SEQ ID NO 176**
**LENGTH: 21**
**TYPE: DNA**
**ORGANISM: Artificial Sequence**
**FEATURE:**
**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
**FEATURE:**
**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**SEQUENCE:** 176

aaucgagaa gacgccgcaat t

**SEQ ID NO 177**
**LENGTH: 21**
**TYPE: DNA**
**ORGANISM: Artificial Sequence**
**FEATURE:**
**OTHER INFORMATION:** Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
**FEATURE:**
**OTHER INFORMATION:** Description of Artificial Sequence: Synthetic oligonucleotide

**SEQUENCE:** 177

gaggggcga aacuauaact t

**SEQ ID NO 178**
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**FEATURE:**
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**SEQUENCE:** 178

gguauaggu augcaccuact t
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<400> SEQUENCE: 189
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<400> SEQUENCE: 194

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oligonucleotide

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oligonucleotide

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SEQ ID NO 203
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
SEQUENCE: 203

cuac guaac aacg gaaat t

21

SEQ ID NO 204
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
SEQUENCE: 204

uuuc gguu ug uac gug ugt t

21

SEQ ID NO 205
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
SEQUENCE: 205

ucgc uauu c ugug ugt t

21

SEQ ID NO 206
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
SEQUENCE: 206

ca ca gcu a c gua a g t

21

SEQ ID NO 207
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
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aguuaauau uucgaggt t

cuucgcgc uuacuccgt t

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uuucgccguu uagugcoac t

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oligonucleotide

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<400>SEQUENCE: 232

uguuaaauuc gagggact t

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 245

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<400> SEQUENCE: 246

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21

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<400> SEQUENCE: 265

aaauucuggc cuucacccct t 21

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<400> SEQUENCE: 266

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<400> SEQUENCE: 267

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<220> FEATURE:
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<400> SEQUENCE: 366

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<400> SEQUENCE: 367

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<400> SEQUENCE: 368

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ccgauggcu uguuggucut t

cuccuuaag gcuccuuuct t

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<400> SEQUENCE: 374
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SEQUENCE: 378
ucacuaggg gcgcgcggtu t

SEQ ID NO: 379
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TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 379
accgcgcgcc acacuagaggt t

SEQ ID NO: 380
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 380
cucacuagug gcgcgcggtu t

SEQ ID NO: 381
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 381
gcugucgaug ucucgcgcaut t

SEQ ID NO: 382
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 382
augcogacag aucgcacagct t

SEQ ID NO: 383
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQ: 383
ucgaugucg ggcuaucgat t

SEQ: 384
ucgaugccg agcaucgat t

SEQ: 385
ucguaggcau gcaucgaggt t

SEQ: 386
ucgucaucau augcgcgat t

SEQ: 387
ggcuaucgau gcagcaaat t
uuguccgca ugaauagct t

21

uuguccgga ugaauagct t

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uuguccgga ugaauagct t

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uuguccgga ugaauagct t

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GUUUGAAG CUCCUCAGT

GUACUGAU UGGGAUGCT

GCAUCCSC AGUCAUACT

AGCAAAUCU CUUUGGCCU

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GUACUGAU UGGGAUGCT

GCAUCCSC AGUCAUACT

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<400> SEQUENCE: 403

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<400> SEQUENCE: 404

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<400> SEQUENCE: 406

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<400> SEQUENCE: 408
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SEQUENCE: 416

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SEQ ID NO: 417
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 417

uagaccuaaua cauauuauut t  21

SEQ ID NO: 418
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 418

aaauuaagugu augguugat t  21

SEQ ID NO: 419
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 419

cuaucacuguc acugugagut t  21

SEQ ID NO: 420
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 420

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ORGANISM: Artificial Sequence
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<400> SEQUENCE: 421
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<400> SEQUENCE: 422
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<400> SEQUENCE: 423
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<400> SEQUENCE: 424
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<400> SEQUENCE: 425
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uaccguacca accgaaaaat t

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uauuuuuuc guuguaacgt t

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<210> SEQ ID NO 433
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<210> SEQ ID NO 434
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aaaaccaua uguacuauct t

21

gaugagcua augauuuuut t

21

cuguuacag ccuacuauut t

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auacacgcu guuacacagt t

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 SEQUENCE: 436
 aaugacgcc cgauagaccat t  21

 SEQUENCE: 437
 ccucguauau gcacuccuuu t  21

 SEQUENCE: 438
 aaaggucau aaagcaggt t  21

 SEQUENCE: 439
 ggcccaugua ccaacaggt t  21

 SEQUENCE: 440

ccguuaggu acaagggcct t 21

ccauacucc aaccagcuut t 21

agccguuuu guacgauggt t 21

ccguuacua ucgucaauat t 21

auuacgcag uagcuacugt t 21
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<400> SEQUENCE: 445
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<400> SEQUENCE: 446
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<400> SEQUENCE: 447
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<210> SEQ ID NO 448
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<220> FEATURE:
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<400> SEQUENCE: 448
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<400> SEQUENCE: 449
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<210> SEQ ID NO 450
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<400> SEQUENCE: 450

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<400> SEQUENCE: 451

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<400> SEQUENCE: 452

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<400> SEQUENCE: 453

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
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<400> SEQUENCE: 455

gcgcacacugcuacucugctt

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<400> SEQUENCE: 457

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<400> SEQUENCE: 458

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<400> SEQUENCE: 459

cgaacgcgugcagcucucugctt
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<400> SEQUENCE: 459

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<400> SEQUENCE: 460
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<210> SEQ ID NO 461
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 461
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<210> SEQ ID NO 462
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<400> SEQUENCE: 462
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<210> SEQ ID NO 463
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<400> SEQUENCE: 463
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<400> SEQUENCE: 464

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SEQUENCE: 478

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TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 479

uuuguaaug uugcauggct t

SEQ ID NO 480
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 480

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SEQ ID NO 481
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 481

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SEQ ID NO 482
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
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FEATURE:
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SEQUENCE: 482

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<400> SEQUENCE: 501

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ccauugcag ccuauuuut
aaaauagagc ugcuauggt t

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SEQUENCE: 511
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TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 512
gauagaauauauccauugttt 21

SEQ ID NO 513
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 513
asauagaaauauacgaucctt 21

SEQ ID NO 514
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 514
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SEQ ID NO 515
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 515
ucgaaauauauacgcaagt 21

SEQ ID NO 516
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 516

cuggauca guauuucgat t

SEQ ID NO 517
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 517

saaccaacu ugasccacau t

SEQ ID NO 518
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 519

aaugguaua aggaugauut t

SEQ ID NO 519
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 519

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SEQ ID NO 520
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

SEQUENCE: 520

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<400> SEQUENCE: 521

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<400> SEQUENCE: 527
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<400> SEQUENCE: 530

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<210> SEQ ID NO 547
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 547
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<210> SEQ ID NO 548
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 548
aaggsagggag gtttgatacg tgcgttttttc tcttgaaag aaagt 45

<210> SEQ ID NO 549
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 549
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<210> SEQ ID NO 550
<211> LENGTH: 47
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 550
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<210> SEQ ID NO 551
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 551
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<210> SEQ ID NO 552
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 552
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<210> SEQ ID NO 553
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 553
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<210> SEQ ID NO 554
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 554
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<210> SEQ ID NO 555
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 555
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<210> SEQ ID NO 556
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 556
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cagagcaggt ggacacttct ttttaggcat aggacccgtg tct 43

tgtggaggtg ggagaggtt g 21

cctctgaca ctttgctgtt tatt 24

ggtgattgtg tgtctctctgt ggag 24

ggtgattgtg tgtctctctgt ggag 24
gctgaaaa gacatctgc g
21

<210> SEQ ID NO 563
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 563

gccagggac ggaaatgg
19

<210> SEQ ID NO 564
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 564

ccctcaggga gtagatgatcg
23

<210> SEQ ID NO 565
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 565

ggaagactc catca tgtgact
24

<210> SEQ ID NO 566
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 566

tctaggagg ggcccttg
18

<210> SEQ ID NO 567
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 567

gcggggtggtg ttcatctctct c
21

<210> SEQ ID NO 568
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 568
gcagcctcag tsgtggygc

<210> SEQ ID NO 569
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 569
tcgtgctgaca agaaaagctt ctttt

<210> SEQ ID NO 570
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 570
cccggagaaag ttcatctaaag tat

<210> SEQ ID NO 571
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 571
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g

<210> SEQ ID NO 572
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 572
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<210> SEQ ID NO 573
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 573
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<210> SEQ ID NO 574
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 574

gtcgcccccct gcatactgttttctcttg gaagaagaag

40

<210> SEQ ID NO 575
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 575

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42

<210> SEQ ID NO 576
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 576

gatgacaagctccgctctcttttaggc ataggacccgt tgtct

45

<210> SEQ ID NO 577
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 577

agatggtgatggatttctacttttaggc ataggacccgt tgtct

46

<210> SEQ ID NO 578
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 578

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44

<210> SEQ ID NO 579
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 579

cagcagctac tcagccgcat tttaggcat agaccctgtctc

43

<210> SEQ ID NO 580
<211> LENGTH: 46
<212> TYPE: DNA
<210> SEQ ID NO 581
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 581

gggagagatg atgaccccttt ttgtttttagg ctaggaacc cgtgtct 46

<210> SEQ ID NO 582
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 582

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<210> SEQ ID NO 583
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 583

gggacgtgt cccccccatt ttctcttgg aaagaagt 39

<210> SEQ ID NO 584
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 584
tcgctgagca aagtgaaatt ttctctttgg aaagaagt 39

<210> SEQ ID NO 585
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 585
tctcgcttt ccccgagtt ttctctttgg aaagaagt 38

<210> SEQ ID NO 586
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 586

cgggaccttg gctgtctttt ttctcttggg aagaaagt

<211> SEQ ID NO 587
<212> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 587

ttttgcctgg ggggcttggg ttctcttggg aagaaagt

<211> SEQ ID NO 588
<212> LENGTH: 47
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 588

ggtgtgagatc attcattgtc ctgatctttag gcataggacc ggtgtct

<211> SEQ ID NO 589
<212> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 589

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<211> SEQ ID NO 590
<212> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 590

aatgatcctg cggctgttttt ttaggcata gaccggtgct t

<211> SEQ ID NO 591
<212> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 591

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<210> SEQ ID NO 592
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 592

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<210> SEQ ID NO 593
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 593

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<210> SEQ ID NO 594
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 594

ccccctggtgctcgcagcttttaggcataggaccgtgctt 41

<210> SEQ ID NO 595
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 595

cactctcagttcctgagaatc 24

<210> SEQ ID NO 596
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 596

ggaccatctttctgggtcagaattg 24

<210> SEQ ID NO 597
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 597

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<210> SEQ ID NO 598
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 598
aacgtagctt catgagatct cc

<210> SEQ ID NO 599
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 599
tggtgtgcttt tcattcatctg caa

<210> SEQ ID NO 600
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 600
cacgacatgc tggtagtggg

<210> SEQ ID NO 601
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 601
gcacgggccag ggcac

<210> SEQ ID NO 602
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 602
tgcagctcaag agtgcagtcc t

<210> SEQ ID NO 603
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<400> SEQUENCE: 603

ggtctcctgg ggtatggg 10

<210> SEQ ID NO 604
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)...(21)
<223> OTHER INFORMATION: 2'-O-(2-methoxyethyl) thymidine
<400> SEQUENCE: 604
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<210> SEQ ID NO 605
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)...(20)
<223> OTHER INFORMATION: 2'-O-(2-methoxyethyl) cytidine
<220> FEATURE:
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<222> LOCATION: (21)...(21)
<223> OTHER INFORMATION: 2'-O-(2-methoxyethyl) thymidine
<400> SEQUENCE: 605
gcaauugguu cauaggaugc t 21

<210> SEQ ID NO 606
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (4)...(5)
<223> OTHER INFORMATION: 2'-O-methylcytidine-5'-phosphate
<220> FEATURE:
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<222> LOCATION: (6)...(6)
<223> OTHER INFORMATION: 2'-O-methyluridine-5'-phosphate
<220> FEATURE:
caucauaag accaaugct t 21

gcuauuggu caausaugt t 21
We claim:

1. A double-stranded ribonucleic acid (dsRNA) for inhibiting the expression of a human Nav1.8 gene in a cell, wherein said dsRNA comprises at least two sequences that are complementary to each other and wherein a sense strand comprises a first sequence and an antisense strand comprises a second sequence comprising a region of complementarity which is substantially complementary to at least a part of a mRNA encoding Nav1.8, and wherein said region of complementarity is less than 30 nucleotides in length and wherein said dsRNA, upon contact with a cell expressing said Nav1.8, inhibits expression of said Nav1.8 gene by at least 20%.

2. The dsRNA of claim 1, wherein said first sequence is selected from the group consisting of Tables 1, 4 and 6 and said second sequence is selected from the group consisting of Tables 1, 4 and 6.

3. The dsRNA of claim 1, wherein said dsRNA comprises at least one modified nucleotide.

4. The dsRNA of claim 2, wherein said dsRNA comprises at least one modified nucleotide.

5. The dsRNA of claim 3, wherein said modified nucleotide is chosen from the group of: a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bis decyclamide group.

6. The dsRNA of claim 3, wherein said modified nucleotide is chosen from the group of: a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-amino-modified nucleotide, 2'-O-alkyl-modified nucleotide, morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

7. A cell comprising the dsRNA of claim 1.

8. A pharmaceutical composition for inhibiting the expression of the Nav1.8 gene in an organism, comprising a dsRNA and a pharmaceutically acceptable carrier, wherein the
dsRNA comprises at least two sequences that are complementary to each other and wherein a sense strand comprises a first sequence and an antisense strand comprises a second sequence comprising a region of complementarity which is substantially complementary to at least a part of a mRNA encoding Nav1.8, and wherein said region of complementarity is less than 30 nucleotides in length and wherein said dsRNA, upon contact with a cell expressing said Nav1.8, inhibits expression of said Nav1.8 gene by at least 20%.

9. The pharmaceutical composition of claim 8, wherein said first sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6 and said second sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6.

10. The pharmaceutical composition of claim 9, wherein said composition is formulated for administration selected from the group consisting of intrathecal infusion or injection, or intravenous infusion or injection.

11. A method for inhibiting the expression of the Nav1.8 gene in a cell, the method comprising:
   (a) introducing into the cell a double-stranded ribonucleic acid (dsRNA), wherein the dsRNA comprises at least two sequences that are complementary to each other and wherein a sense strand comprises a first sequence and an antisense strand comprises a second sequence comprising a region of complementarity which is substantially complementary to at least a part of a mRNA encoding Nav1.8, and wherein said region of complementarity is less than 30 nucleotides in length and wherein said dsRNA, upon contact with a cell expressing said Nav1.8, inhibits expression of said Nav1.8 gene by at least 20%; and
   (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the Nav1.8 gene, thereby inhibiting expression of the Nav1.8 gene in the cell.

12. The method of claim 11, wherein said first sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6 and said second sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6.

13. A method of treating, preventing or managing pain comprising administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a dsRNA, wherein the dsRNA comprises at least two sequences that are complementary to each other and wherein a sense strand comprises a first sequence and an antisense strand comprises a second sequence comprising a region of complementarity which is substantially complementary to at least a part of a mRNA encoding Nav1.8, and wherein said region of complementarity is less than 30 nucleotides in length and wherein said dsRNA, upon contact with a cell expressing said Nav1.8, inhibits expression of said Nav1.8 gene by at least 20%.

14. The method of claim 13, wherein said first sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6 and said second sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6.

15. The method of claim 14, wherein said pain is selected from the group consisting of neuropathic pain and inflammatory pain.

16. A vector for inhibiting the expression of the Nav1.8 gene in a cell, said vector comprising a regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of a dsRNA, wherein one of the strands of said dsRNA is substantially complementary to at least a part of a mRNA encoding Nav1.8 and wherein said dsRNA is less than 30 base pairs in length and wherein said dsRNA, upon contact with a cell expressing said Nav1.8, inhibits the expression of said Nav1.8 gene by at least 20%.

17. The vector of claim 16, wherein said first sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6 and said second sequence of said dsRNA is selected from the group consisting of Tables 1, 4 and 6.

18. A cell comprising the vector of claim 16.

19. A cell comprising the vector of claim 17.