



US 20100317718A1

(19) **United States**

(12) **Patent Application Publication**
Marcusson et al.

(10) **Pub. No.: US 2010/0317718 A1**

(43) **Pub. Date: Dec. 16, 2010**

(54) **MODULATION OF HIF1 BETA EXPRESSION**

(75) Inventors: **Eric G. Marcusson**, San Deigo, CA
(US); **Scott Henry**, Cardiff, CA
(US); **Youngsoo Kim**, San Diego,
CA (US); **Kenneth W. Dobie**, Del
Mar, CA (US)

Correspondence Address:

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET, FOURTEENTH FLOOR
IRVINE, CA 92614 (US)

(73) Assignee: **Isis Pharmaceuticals, Inc.**,
Carlsbad, CA (US)

(21) Appl. No.: **12/846,746**

(22) Filed: **Jul. 29, 2010**

Related U.S. Application Data

(63) Continuation of application No. 12/578,468, filed on
Oct. 13, 2009, now Pat. No. 7,799,764, which is a
continuation of application No. 11/213,593, filed on
Aug. 25, 2005, now Pat. No. 7,618,947.

(60) Provisional application No. 60/604,190, filed on Aug.
25, 2004, provisional application No. 60/649,586,
filed on Feb. 2, 2005.

Publication Classification

(51) **Int. Cl.**

A61K 31/7125 (2006.01)

C07H 21/00 (2006.01)

A61K 31/712 (2006.01)

A61K 31/7115 (2006.01)

A61P 35/00 (2006.01)

A61P 27/02 (2006.01)

(52) **U.S. Cl. 514/44 A; 536/23.1**

(57) **ABSTRACT**

Compounds, compositions and methods are provided for
modulating the expression of HIF1-beta. The compositions
comprise oligonucleotides, targeted to nucleic acid encoding
HIF1-beta. Methods of using these compounds for modula-
tion of HIF1-beta expression and for diagnosis and treatment
of diseases and conditions associated with expression of
HIF1-beta are provided.

MODULATION OF HIF1 BETA EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 12/578,468, filed Oct. 13, 2009, which is a continuation of U.S. patent application Ser. No. 11/213,593, filed Aug. 25, 2005, now U.S. Pat. No. 7,618,947, which claims the benefit of priority to U.S. provisional patent application Ser. No. 60/604,190, filed Aug. 25, 2004, and U.S. provisional patent application Ser. No. 60/649,586, filed Feb. 2, 2005, all of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention provides compositions and methods for modulating the expression of HIF1-beta. In particular, this invention relates to antisense compounds, particularly oligonucleotide compounds, which, in preferred embodiments, hybridize with nucleic acid molecules encoding HIF1-beta. Such compounds are shown herein to modulate the expression of HIF1-beta.

BACKGROUND OF THE INVENTION

[0003] Oxygen homeostasis in mammals is tightly regulated, necessitated by the need to maintain sufficient levels for critical oxygen-dependent processes while minimizing the production of oxygen reactive species that are capable of causing oxidative damage to DNA, lipids, and proteins. In a state of hypoxia, where oxygen demand exceeds supply, a physiological response is mounted that increases the capacity of blood to carry oxygen to tissues and alters cellular metabolism, such as facilitating ATP production by anaerobic glycolysis. The hypoxia-inducible factors (HIFs) are key transcriptional regulators of this hypoxic response. These factors have also been implicated in the pathology of many major human diseases, including cancer, myocardial infarction, ischemia and preeclampsia (Harris, *Nat. Rev. Cancer*, 2002, 2, 38-47); (Lee et al., *N Engl J Med*, 2000, 342, 626-633); (Aplin, *J Clin Invest*, 2000, 105, 559-560). Cells are typically cultured in the laboratory at an ambient oxygen concentration of 21%, but cells in the human body are exposed to much lower oxygen concentrations ranging from 16% in the lungs to less than 6% in most other organs of the body and often significantly less in tumors (Semenza, *Trends Mol Med*, 2001, 7, 345-350).

[0004] The HIF proteins are heterodimers consisting of HIF1-beta and one of three alpha subunits, HIF1-alpha, HIF2-alpha and HIF3-alpha (Safran and Kaelin, *J. Clin. Invest.*, 2003, 111, 779-783). The discovery of the HIF proteins was enabled by the identification of a minimal hypoxia-responsive element (HRE) in the 3' enhancer of the erythropoietin gene (Wang and Semenza, *Proc Natl Acad Sci USA*, 1993, 90, 4304-4308). Subsequent analysis identified the HIF protein as a phosphorylation-dependent protein that binds DNA under hypoxic conditions (Wang and Semenza, *J Biol Chem*, 1993, 268, 21513-21518). Purification of this DNA-binding factor revealed HIF was a heterodimeric complex consisting of a novel protein, HIF1-alpha, and the aryl hydrocarbon nuclear translocator (ARNT, also termed HIF1-beta), previously identified as a binding partner of the dioxin/aryl hydrocarbon receptor (Wang and Semenza, *J. Biol. Chem.*, 1995, 270, 1230-1237); (Hoffman et al., *Science*, 1991, 252,

954-958). HIF proteins belong to a class of transcription factors termed basic helix-loop-helix proteins, grouped by two conserved domains. The basic region consists of approximately 15 predominantly basic amino acids responsible for direct DNA binding. This region is adjacent to two amphipathic alpha helices, separated by a loop of variable length, which forms the primary dimerization interface between family members (Moore et al., *Proc Natl Acad Sci USA*, 2000, 97, 10436-10441).

[0005] HIF1-beta is a key player in two major signaling pathways, the hypoxic-response pathway and the aryl hydrocarbon receptor (AHR) pathway. Since the discovery of HIF1-alpha/HIF1-beta involvement in erythropoietin transcription, HIF activity has been detected in various non-erythropoietin-producing cell lines cultured under hypoxic conditions (Wang and Semenza, *Proc Natl Acad Sci USA*, 1993, 90, 4304-4308); (Maxwell et al., *Proc Natl Acad Sci USA*, 1993, 90, 2423-2427), providing the first evidence that the HIF1 dimer not only activates the erythropoietin gene, but is part of a widespread oxygen-sensing and signal transduction mechanism. Under normoxic conditions, HIF1-alpha is rapidly degraded due to the oxygen-dependent hydroxylation of specific proline residues that mark the protein for proteasomal degradation (Jewell et al., *Faseb J*, 2001, 15, 1312-1314); (Gorlach et al., *Biochim Biophys Acta*, 2000, 1493, 125-134). Under hypoxic conditions, this hydroxylation is reversed, and the protein is further stabilized by phosphorylation (Wang et al., *Biochem Biophys Res Commun*, 1995, 216, 669-675). Subsequently, the protein is translocated to the nucleus, where it interacts with HIF1-beta to form a heterodimeric transcription factor (Kallio et al., *Embo J*, 1998, 17, 6573-6586). Studies in HIF1-beta deficient cells revealed an absolute requirement for this dimerization step for the transcriptional activation of hypoxia response element genes (Wood et al., *J Biol Chem*, 1996, 271, 15117-15123). Categories of genes that are activated by the HIF1 dimer include oxygen transport genes, such as erythropoietin (Semenza et al., *J Biol Chem*, 1994, 269, 23757-23763) and transferrin (Rolfis et al., *J Biol Chem*, 1997, 272, 20055-20062); genes involved in angiogenesis, such as VEGF (Levy et al., *J Biol Chem*, 1995, 270, 13333-13340); and genes involved in anaerobic metabolism, such as glucose transporter 1 (Ebert et al., *J Biol Chem*, 1995, 270, 29083-29089). Hypoxia-induced genes such as VEGF are thought to play a role in promoting angiogenesis and subsequent tumor growth (Harris, *Nat. Rev. Cancer*, 2002, 2, 38-47).

[0006] HIF transcriptional activity is precisely regulated by cellular oxygen concentration. Whereas changes in oxygen levels do not affect HIF1-beta protein levels, the abundance of the HIF-alpha subunits is markedly increased upon exposure of cells to hypoxia, primarily due to stabilization of the alpha subunits (Safran and Kaelin, *J. Clin. Invest.*, 2003, 111, 779-783). HIF2-alpha mRNA and protein is expressed at low levels in tissue culture cells, but protein expression is markedly induced by exposure to 1% oxygen, a hypoxic state (Wiesener et al., *Blood*, 1998, 92, 2260-2268). The HIF2-alpha/HIF1-beta heterodimer protein binds to the hypoxic response element, which contains the core recognition sequence 5'-TACGTG-3' and is found in the cis-regulatory regions of hypoxia-regulated genes (Ema et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1997, 94, 4273-4278); (Hogenesch et al., *J. Biol. Chem.*, 1997, 272, 8581-8593). Binding of the heterodimer to the HRE induces gene expression (Wiesener et al., *Blood*, 1998, 92, 2260-2268).

[0007] In contrast to the HIF- α subunits, HIF1- β is stable under both hypoxic and normoxic conditions, and also participates in the aryl hydrocarbon receptor (AHR) signaling pathway. AHR is a cytoplasmic receptor protein that translocates to the nucleus after ligand binding. Ligands of AHR include 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), an environmental toxin that is a by-product of industrial processes (Poland et al., *J Biol Chem*, 1976, 251, 4936-4946); polycyclic aromatic hydrocarbons, found in cigarette smoke and smog (Reisz-Porszasz et al., *Mol Cell Biol*, 1994, 14, 6075-6086); and heterocyclic amines, found in some cooked meats (Reisz-Porszasz et al., *Mol Cell Biol*, 1994, 14, 6075-6086). After ligand-binding and nuclear translocation, AHR forms a dimer with HIF1- β , resulting in the activation of a number of genes involved in drug metabolism, such as the cytochromes P450, CYP1A1, CYP1A2, and CYP1B1. AHR/HIF1- β dimers are capable of activating a range of other genes regulated by the dioxin response element (DRE), resulting in some of the toxic and carcinogenic effects associated with many of the AHR ligands, such as immunotoxicity, developmental and reproductive toxicity, disruption of endocrine pathways, a wasting syndrome, and tumor promotion (Safe, *Toxicol Lett*, 2001, 120, 1-7). Ohtake and colleagues (Ohtake et al., *Nature*, 2003, 423, 545-550) demonstrated that the AHR/HIF1- β heterodimer directly associates with the estrogen receptors ER- α and ER- β . They showed that this association results in the recruitment of unliganded estrogen receptor and coactivator p300 to estrogen-responsive gene promoters, leading to activation of transcription and estrogenic effects and giving rise to the adverse estrogen-related actions of dioxin-type environmental contaminants.

[0008] The role of HIF1- β in both hypoxia-induced and AHR signaling pathways makes it an attractive therapeutic candidate, as both of these pathways have been linked to various forms of malignancies (Harris, *Nat. Rev. Cancer*, 2002, 2, 38-47); (Safe, *Toxicol Lett*, 2001, 120, 1-7). The angiogenic promoting capabilities of HIF1- β also mark this gene as a potential therapeutic target for a variety of angiogenic disorders, such as arthritis, cardiovascular diseases, skin conditions, aberrant wound healing and ocular conditions (e.g., macular degeneration, diabetic retinopathy, diabetic macular edema and retinopathy of prematurity).

[0009] PCT publication WO 02/053735 discloses the use of an oligonucleotide 35 nucleotides in length as a PCR primer for amplification of the HIF1- β sequence.

[0010] U.S. Pat. No. 6,352,829 discloses the use of an oligonucleotide 26 nucleotides in length as a PCR primer for amplification of the HIF1- β sequence.

[0011] U.S. pre-grant publication 2004-0152655 discloses antisense oligonucleotide compounds for inhibiting HIF1- α .

[0012] U.S. pre-grant publication 2004-0096848 discloses oligomeric compounds directed against HIF1- α .

[0013] U.S. pre-grant publication 2005-0163781 discloses compounds for use as inhibitors of hypoxia-induced genes, such as HIF1- α and HIF2- α , to treat adhesion formation.

[0014] U.S. pre-grant publication 2004-0180357 discloses HIF1- α siRNA compounds for downregulating expression of HIF1- α and VEGF and inhibiting angiogenesis.

[0015] U.S. pre-grant publication 2005-0148496 discloses methods of treating inflammatory disorders such as rheumatoid arthritis using compounds that inhibit HIF1- α activity.

[0016] U.S. pre-grant publication 2004-0086498 discloses methods for treating animals with advanced or large tumor burdens by administration of an immunotherapeutic agent and a tumor growth restricting agent, such as an expression vector encoding an antisense version of HIF1- α .

[0017] U.S. pre-grant publication 2005-0070474 discloses methods of treating tumors using an agent to increase B7-H3 in combination with an agent to inhibit HIF1- α , HIF2- α or HIF3- α .

[0018] Currently, there are no known therapeutic agents which effectively inhibit the synthesis of HIF1- β and to date, investigative strategies aimed at modulating the function of HIF1- β have involved the use of antibodies and inactive mutants. Consequently, there remains a long felt need for additional agents capable of effectively inhibiting HIF1- β function.

[0019] Antisense technology is an effective means for reducing the expression of specific gene products and may therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications for the modulation of HIF1- β expression. Provided herein are antisense compounds for inhibition of HIF1- β expression. The disclosed compounds can be used for treating or preventing conditions associated with HIF1- β , such as cancer and angiogenic disorders.

SUMMARY OF THE INVENTION

[0020] The present invention is directed to antisense compounds, especially nucleic acid and nucleic acid-like oligomers, which are targeted to a nucleic acid encoding HIF1- β , and which modulate the expression of HIF1- β . Pharmaceutical and other compositions comprising the compounds of the invention and methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of HIF1- β are also set forth herein.

[0021] Provided herein are antisense oligonucleotides which are specifically hybridizable with a nucleic acid molecule encoding human HIF1- β . The HIF1- β antisense oligonucleotides comprise at least one internucleoside, sugar or nucleobase modification. Contemplated are oligonucleotides 13 to 80, 13 to 50, 13 to 30, 20 to 30, 15 to 25 or 20 nucleobases in length. In one embodiment, the internucleoside modification is a phosphorothioate. In one embodiment, the modified sugar moiety is a 2'-O-(2-methoxyethyl). In one embodiment, the modified nucleobase is a 5-methyl cytosine. In some embodiments, the HIF1- β antisense oligonucleotides further comprise a complementary strand. Also provided are antisense oligonucleotides which specifically hybridize to a splice variant of human HIF1- β .

[0022] In one embodiment, the antisense oligonucleotides comprise at least an 8-nucleobase portion of one of the illustrative antisense oligonucleotides provided herein. In one embodiment, the antisense oligonucleotide is specifically hybridizable with at least a portion of a start codon region of human HIF1- β . In another embodiment, the antisense oligonucleotide comprises at least an 8-nucleobase portion of SEQ ID NO: 30. In one embodiment, the antisense oligonucleotide is specifically hybridizable with at least a portion of nucleotides 1876-1895 of a coding region of human HIF1-

beta. In another embodiment, the antisense oligonucleotide comprises at least an 8-nucleobase portion of SEQ ID NO: 77.

[0023] Further provided are chimeric antisense oligonucleotides which are specifically hybridizable with a nucleic acid molecule encoding human HIF1-beta. In one embodiment, the chimeric antisense oligonucleotides have a first region comprising deoxynucleotides and second and third regions flanking the first region comprising at least one 2'-O-(2-methoxyethyl) nucleotide. In some embodiments, the first region is 10 deoxynucleotides in length and the second and third regions are each 5 nucleotides in length. The chimeric antisense oligonucleotides provided herein may further comprise a phosphorothioate linkage at each position.

[0024] Also provided are pharmaceutical compositions comprising the antisense oligonucleotides of the invention and a pharmaceutically acceptable carrier or diluent. Pharmaceutical compositions further comprising a colloidal dispersion system are also provided.

[0025] The present invention also provides methods of inhibiting expression of human HIF1-beta in cells or tissues by contacting the cells or tissues with one or more of the compounds provided herein such that expression is inhibited. In one embodiment, HIF1-beta expression is inhibited by 20%. In another embodiment, HIF1-beta expression is inhibited by 40%. In another embodiment, HIF1-beta expression is inhibited by 50%. In another embodiment, HIF1-beta expression is inhibited by 60%. In another embodiment, HIF1-beta expression is inhibited by 70%. In another embodiment, HIF1-beta expression is inhibited by 80%. In one embodiment, the compounds used to inhibit expression of human HIF1-beta comprise at least an 8-nucleobase portion of SEQ ID NO: 30. In another embodiment, the compounds used to inhibit expression of human HIF1-beta comprise at least an 8-nucleobase portion of SEQ ID NO: 77.

[0026] Also provided are methods of inhibiting expression of HIF1-beta regulated genes in cells or tissues by contacting the cells or tissues with one or more of the compounds provided herein. In one embodiment, the HIF1-beta regulated gene is VEGF. In another embodiment, the HIF1-beta regulated gene is GLUT-1. In another embodiment, the HIF1-beta regulated gene is PGK-1. In another embodiment, the HIF1-beta regulated gene is PAI-1. In yet another embodiment, the HIF1-beta regulated gene is Epo.

[0027] Further provided are methods of treating an animal having a disease or condition associated with HIF1-beta comprising administering to the animal a therapeutically or prophylactically effective amount of a composition comprising one of more of the antisense oligonucleotides provided herein. In one embodiment, the disease or condition associated with HIF1-beta is a hyperproliferative disorder. In one aspect, the hyperproliferative disorder is cancer. In another aspect, the hyperproliferative disorder is an angiogenic disorder. In further embodiments, the angiogenic disorder is an ocular disorder. Ocular disorders contemplated herein, include, but are not limited to macular degeneration, diabetic retinopathy, macular edema and retinopathy of prematurity. In one embodiment, the compounds used to treat the disease or disorder comprise at least an 8-nucleobase portion of SEQ ID NO: 30. In another embodiment, the compounds used to treat the disease or disorder comprise at least an 8-nucleobase portion of SEQ ID NO: 77.

[0028] Also provided are methods of treating an animal having a disease or condition associated with a HIF1-beta regulated gene by administering to the animal a therapeuti-

cally or prophylactically effective amount of a composition comprising one or more of the HIF1-beta antisense oligonucleotides provided herein. In one embodiment, the disease or condition is a hyperproliferative disorder. In a further embodiment, the hyperproliferative disorder is an angiogenic disorder.

[0029] The present invention also provides methods of preventing or inhibiting aberrant angiogenesis in an animal, methods of inhibiting tumor growth in an animal and methods of preventing or inhibiting ocular neovascularization in an animal, comprising administering to said animal one or more of the antisense oligonucleotides provided herein.

[0030] In one embodiment of the methods, the antisense oligonucleotides comprise at least an 8-nucleobase portion of one of the illustrative antisense oligonucleotides provided herein.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0031] HIF1-beta is known to play an important role in cellular signaling pathways that can contribute to a number of medically-important pathologic conditions such as cancer and disorders arising from aberrant angiogenesis. To date, there are no effective means for inhibition of HIF1-beta expression. Thus, disclosed herein are antisense compounds for modulation of HIF1-beta expression. The compounds of the invention can be used, for example, to inhibit or prevent aberrant angiogenesis, inhibit tumor growth, or inhibit expression of HIF1-beta regulated genes.

[0032] As used herein, "aberrant angiogenesis" refers to unwanted or uncontrolled angiogenesis.

[0033] As used herein, "targeting" or "targeted to" refer to the process of designing an oligomeric compound such that the compound hybridizes with a selected nucleic acid molecule or region of a nucleic acid molecule.

[0034] As used herein, "hybridization" means the pairing of complementary strands of oligomeric compounds. In the context of the present invention, an oligomeric compound is "specifically hybridizable" when there is a sufficient degree of complementarity to avoid non-specific binding of the oligomeric compound to non-target nucleic acid sequences. One of skill in the art will be able to determine when an oligomeric compound is specifically hybridizable.

[0035] As used herein, a "HIF1-beta regulated gene" is a gene whose expression is modulated by HIF1-beta gene products.

[0036] The present invention employs antisense compounds, preferably oligonucleotides and similar species for use in modulating the function or effect of nucleic acid molecules encoding HIF1-beta. This is accomplished by providing oligonucleotides which specifically hybridize with one or more nucleic acid molecules encoding HIF1-beta. As used herein, the terms "target nucleic acid" and "nucleic acid molecule encoding HIF1-beta" have been used for convenience to encompass DNA encoding HIF1-beta, RNA (including pre-mRNA and mRNA or portions thereof) transcribed from such DNA, and also cDNA derived from such RNA. The hybridization of a compound of this invention with its target nucleic acid is generally referred to as "antisense". Consequently, the preferred mechanism believed to be included in the practice of some preferred embodiments of the invention is referred to herein as "antisense inhibition." Such antisense inhibition is typically based upon hydrogen bonding-based hybridization of oligonucleotide strands or segments such that at least one

strand or segment is cleaved, degraded, or otherwise rendered inoperable. In this regard, it is presently preferred to target specific nucleic acid molecules and their functions for such antisense inhibition.

[0037] The functions of DNA to be interfered with can include replication and transcription. Replication and transcription, for example, can be from an endogenous cellular template, a vector, a plasmid construct or otherwise. The functions of RNA to be interfered with can include functions such as translocation of the RNA to a site of protein translation, translocation of the RNA to sites within the cell which are distant from the site of RNA synthesis, translation of protein from the RNA, splicing of the RNA to yield one or more RNA species, and catalytic activity or complex formation involving the RNA which may be engaged in or facilitated by the RNA. One preferred result of such interference with target nucleic acid function is modulation of the expression of HIF1-beta. In the context of the present invention, "modulation" and "modulation of expression" mean either an increase (stimulation) or a decrease (inhibition) in the amount or levels of a nucleic acid molecule encoding the gene, e.g., DNA or RNA. Inhibition is often the preferred form of modulation of expression and mRNA is often a preferred target nucleic acid.

[0038] In the context of this invention, "hybridization" means the pairing of complementary strands of oligomeric compounds. In the present invention, the preferred mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases (nucleobases) of the strands of oligomeric compounds. For example, adenine and thymine are complementary nucleobases which pair through the formation of hydrogen bonds. Hybridization can occur under varying circumstances.

[0039] An antisense compound is specifically hybridizable when there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target nucleic acid sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and under conditions in which assays are performed in the case of in vitro assays.

[0040] In the present invention, the phrase "stringent hybridization conditions" or "stringent conditions" refers to conditions under which a compound of the invention will hybridize to its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances and in the context of this invention, "stringent conditions" under which oligomeric compounds hybridize to a target sequence are determined by the nature and composition of the oligomeric compounds and the assays in which they are being investigated.

[0041] "Complementary," as used herein, refers to the capacity for precise pairing between two nucleobases of an oligomeric compound. For example, if a nucleobase at a certain position of an oligonucleotide (an oligomeric compound), is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, said target nucleic acid being a DNA, RNA, or oligonucleotide molecule, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be a complementary position. The oligonucleotide and the DNA, RNA, or oligonucleotide molecule are complementary to each other

when a sufficient number of complementary positions in each molecule are occupied by nucleobases which can hydrogen bond with each other. Thus, "specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of precise pairing or complementarity over a sufficient number of nucleobases such that stable and specific binding occurs between the oligonucleotide and a target nucleic acid.

B. Compounds of the Invention

[0042] According to the present invention, antisense compounds include antisense oligomeric compounds, antisense oligonucleotides, siRNAs, ribozymes, external guide sequence (EGS) oligonucleotides, alternate splicers and other oligomeric compounds which hybridize to at least a portion of the target nucleic acid. As such, these compounds may be introduced in the form of single-stranded, double-stranded, circular or hairpin oligomeric compounds and may contain structural elements such as internal or terminal bulges or loops. Once introduced to a system, the compounds of the invention may elicit the action of one or more enzymes or structural proteins to effect modification of the target nucleic acid.

[0043] One non-limiting example of such an enzyme is RNase H, a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-stranded antisense compounds which are "DNA-like" elicit RNase H. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide-mediated inhibition of gene expression. Similar roles have been postulated for other ribonucleases such as those in the RNase III and ribonuclease L family of enzymes.

[0044] While the one form of antisense compound is a single-stranded antisense oligonucleotide, in many species the introduction of double-stranded structures, such as double-stranded RNA (dsRNA) molecules, has been shown to induce potent and specific antisense-mediated reduction of the function of a gene or its associated gene products. This phenomenon occurs in both plants and animals and is believed to have an evolutionary connection to viral defense and transposon silencing.

[0045] The term "oligomeric compound" refers to a polymeric structure capable of hybridizing to a region of a nucleic acid molecule. This term includes oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics and chimeric combinations of these. Oligomeric compounds are routinely prepared linearly but can be joined or otherwise prepared to be circular. Moreover, branched structures are known in the art. An "antisense compound" or "antisense oligomeric compound" refers to an oligomeric compound that is at least partially complementary to the region of a nucleic acid molecule to which it hybridizes and which modulates (increases or decreases) its expression. Consequently, while all antisense compounds can be said to be oligomeric compounds, not all oligomeric compounds are antisense compounds. An "antisense oligonucleotide" is an antisense compound that is a nucleic acid-based oligomer. An antisense oligonucleotide can be chemically modified. Non-limiting examples of oligomeric compounds include primers, probes, antisense compounds, antisense oligonucleotides, external guide sequence (EGS) oligonucleotides and alternate splicers. In one embodiment, the oligomeric compound comprises an antisense strand hybridized to a sense strand.

Oligomeric compounds can be introduced in the form of single-stranded, double-stranded, circular, branched or hair-pins and can contain structural elements such as internal or terminal bulges or loops. Oligomeric double-stranded compounds can be two strands hybridized to form double-stranded compounds or a single strand with sufficient self complementarity to allow for hybridization and formation of a fully or partially double-stranded compound.

[0046] The oligomeric compounds in accordance with this invention comprise compounds from about 8 to about 80 nucleobases (i.e. from about 8 to about 80 linked nucleosides). One of ordinary skill in the art will appreciate that this comprehends antisense compounds of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 nucleobases.

[0047] In one embodiment, the antisense compounds of the invention comprise 13 to 80 nucleobases. One having ordinary skill in the art will appreciate that this embodies antisense compounds of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 nucleobases.

[0048] In one embodiment, the antisense compounds of the invention comprise 13 to 50 nucleobases. One having ordinary skill in the art will appreciate that this embodies antisense compounds of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleobases.

[0049] In one embodiment, the antisense compounds of the invention comprise 13 to 30 nucleobases. One having ordinary skill in the art will appreciate that this embodies antisense compounds of 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleobases.

[0050] In one embodiment, the antisense compounds of the invention comprise 20 to 30 nucleobases. One having ordinary skill in the art will appreciate that this embodies antisense compounds of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases.

[0051] In one embodiment, the antisense compounds of the invention comprise 15 to 25 nucleobases. One having ordinary skill in the art will appreciate that this embodies antisense compounds of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25.

[0052] In one embodiment, the antisense compounds of the invention comprise 20 nucleobases.

[0053] In one embodiment, the antisense compounds of the invention comprise 19 nucleobases.

[0054] In one embodiment, the antisense compounds of the invention comprise 18 nucleobases.

[0055] In one embodiment, the antisense compounds of the invention comprise 17 nucleobases.

[0056] In one embodiment, the antisense compounds of the invention comprise 16 nucleobases.

[0057] In one embodiment, the antisense compounds of the invention comprise 15 nucleobases.

[0058] In one embodiment, the antisense compounds of the invention comprise 14 nucleobases.

[0059] In one embodiment, the antisense compounds of the invention comprise 13 nucleobases.

[0060] Antisense compounds 13-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative antisense compounds are considered to be suitable antisense compounds. Antisense compounds 13-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative antisense compounds are considered to be suitable antisense compounds as well.

[0061] Compounds of the invention include oligonucleotide sequences that comprise at least the 8 consecutive nucleobases from the 5'-terminus of one of the illustrative antisense compounds (the remaining nucleobases being a consecutive stretch of the same oligonucleotide beginning immediately upstream of the 5'-terminus of the antisense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 13 to about 80 nucleobases). Other compounds are represented by oligonucleotide sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative antisense compounds (the remaining nucleobases being a consecutive stretch of the same oligonucleotide beginning immediately downstream of the 3'-terminus of the antisense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 13 to about 80 nucleobases). It is also understood that compounds may be represented by oligonucleotide sequences that comprise at least 8 consecutive nucleobases from an internal portion of the sequence of an illustrative compound, and may extend in either or both directions until the oligonucleotide contains about 13 to about 80 nucleobases.

[0062] One having skill in the art armed with the antisense compounds illustrated herein will be able, without undue experimentation, to identify further antisense compounds.

C. Targets of the Invention

[0063] "Targeting" an antisense compound to a particular nucleic acid molecule, in the context of this invention, can be a multistep process. The process usually begins with the identification of a target nucleic acid whose function is to be modulated. This target nucleic acid may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. In the present invention, the target nucleic acid encodes HIF1-beta.

[0064] The targeting process usually also includes determination of at least one target region, segment, or site within the target nucleic acid for the antisense interaction to occur such that the desired effect, e.g., modulation of expression, will result. Within the context of the present invention, the term "region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic. Within regions of target nucleic acids are segments. "Segments" are defined as smaller or sub-portions of regions within a target nucleic acid. "Sites," as used in the present invention, are defined as positions within a target nucleic acid.

[0065] Suitable target regions include, for example, 3' untranslated region (3'UTR), start codon region, coding region, stop codon region, 5' untranslated region (5' UTR), 5' cap region, exons, introns, intron-exon junctions and exon-exon junctions.

[0066] In the context of the invention, "start codon" and "translation initiation codon" refer to the codon or codons

that are used in vivo to initiate translation of an mRNA transcribed from a gene, regardless of the sequence(s) of such codons. The terms “start codon region” and “translation initiation codon region” refer to a portion of an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation codon. Similarly, the terms “stop codon region” and “translation termination codon region” refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation termination codon. The open reading frame (ORF) or “coding region” is known in the art to refer to the region between the translation initiation codon and the translation termination codon. The 5'UTR refers to the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA (or corresponding nucleotides on the gene), and the 3'UTR refers to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA (or corresponding nucleotides on the gene). The 5' cap site of an mRNA comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage. The 5' cap region of an mRNA is considered to include the 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap site.

[0067] Although some eukaryotic mRNA transcripts are directly translated, many contain one or more regions, known as “introns,” which are excised from a transcript before it is translated. The remaining (and therefore translated) regions are known as “exons” and are spliced together to form a continuous mRNA sequence, resulting in exon-exon junctions at the sites where exons are joined. Targeting exon-exon junctions can be useful in situations where the overproduction of a normal splice product is implicated in disease, or where the overproduction of an aberrant splice product is implicated in disease. Targeting splice sites, i.e., intron-exon junctions or exon-intron junctions, may also be particularly useful in situations where aberrant splicing is implicated in disease, or where an overproduction of a particular splice product is implicated in disease. It is also known that introns can be effectively targeted using antisense compounds targeted to, for example, DNA or pre-mRNA.

[0068] It is also known in the art that alternative RNA transcripts can be produced from the same genomic region of DNA. These alternative transcripts are generally known as “variants”. More specifically, “pre-mRNA variants” are transcripts produced from the same genomic DNA that differ from other transcripts produced from the same genomic DNA in either their start or stop position and contain both intronic and exonic sequence.

[0069] Upon excision of one or more exon or intron regions, or portions thereof during splicing, pre-mRNA variants produce smaller “mRNA variants”. Consequently, mRNA variants are processed pre-mRNA variants and each unique pre-mRNA variant must always produce a unique mRNA variant as a result of splicing. These mRNA variants are also known as “alternative splice variants”. If no splicing of the pre-mRNA variant occurs then the pre-mRNA variant is identical to the mRNA variant.

[0070] It is also known in the art that variants can be produced through the use of alternative signals to start or stop transcription and that pre-mRNAs and mRNAs can possess

more than one start codon or stop codon. Variants that originate from a pre-mRNA or mRNA that use alternative start codons are known as “alternative start variants” of that pre-mRNA or mRNA. Those transcripts that use an alternative stop codon are known as “alternative stop variants” of that pre-mRNA or mRNA. One specific type of alternative stop variant is the “polyA variant” in which the multiple transcripts produced result from the alternative selection of one of the “polyA stop signals” by the transcription machinery, thereby producing transcripts that terminate at unique polyA sites. Within the context of the invention, the types of variants described herein are also preferred target nucleic acids.

[0071] The locations on the target nucleic acid to which the preferred antisense compounds hybridize are referred to as “preferred target segments.” As used herein the term “preferred target segment” is defined as at least an 8-nucleobase portion of a target region to which an active antisense compound is targeted. While not wishing to be bound by theory, it is presently believed that these target segments represent portions of the target nucleic acid which are accessible for hybridization.

[0072] Target segments 13-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within a preferred target segment are considered to be suitable for targeting as well.

[0073] Target segments can include DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 5'-terminus of one of the illustrative preferred target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5'-terminus of the target segment and continuing until the DNA or RNA contains about 13 to about 80 nucleobases). Similarly preferred target segments are represented by DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative preferred target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3'-terminus of the target segment and continuing until the DNA or RNA contains about 13 to about 80 nucleobases). It is also understood that preferred antisense target segments may be represented by DNA or RNA sequences that comprise at least 8 consecutive nucleobases from an internal portion of the sequence of an illustrative preferred target segment, and may extend in either or both directions until the oligonucleotide contains about 13 to about 80 nucleobases. One having skill in the art armed with the preferred target segments illustrated herein will be able, without undue experimentation, to identify further preferred target segments.

[0074] Once one or more target regions, segments or sites have been identified, antisense compounds are chosen which are sufficiently complementary to the target, i.e., hybridize sufficiently well and with sufficient specificity, to give the desired effect.

[0075] The oligomeric antisense compounds can also be targeted to regions of a target nucleobase sequence, such as those disclosed herein.

D. Kits, Research Reagents, Diagnostics, and Therapeutics

[0076] The antisense compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. Furthermore, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill

to elucidate the function of particular genes or to distinguish between functions of various members of a biological pathway.

[0077] For use in kits and diagnostics, the compounds of the present invention, either alone or in combination with other compounds or therapeutics, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of a portion or the entire complement of genes expressed within cells and tissues.

[0078] As one nonlimiting example, expression patterns within cells or tissues treated with one or more antisense compounds are compared to control cells or tissues not treated with antisense compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

[0079] Examples of methods of gene expression analysis known in the art include DNA arrays or microarrays (Brazma and Vilo, *FEBS Lett.*, 2000, 480, 17-24; Celis, et al., *FEBS Lett.*, 2000, 480, 2-16), SAGE (serial analysis of gene expression) (Madden, et al., *Drug Discov. Today*, 2000, 5, 415-425), READS (restriction enzyme amplification of digested cDNAs) (Prashar and Weissman, *Methods Enzymol.*, 1999, 303, 258-72), TOGA (total gene expression analysis) (Sutcliffe, et al., *Proc. Natl. Acad. Sci. U.S.A.*, 2000, 97, 1976-81), protein arrays and proteomics (Celis, et al., *FEBS Lett.*, 2000, 480, 2-16; Jungblut, et al., *Electrophoresis*, 1999, 20, 2100-10), expressed sequence tag (EST) sequencing (Celis, et al., *FEBS Lett.*, 2000, 480, 2-16; Larsson, et al., *J. Biotechnol.*, 2000, 80, 143-57), subtractive RNA fingerprinting (SuRF) (Fuchs, et al., *Anal. Biochem.*, 2000, 286, 91-98; Larson, et al., *Cytometry*, 2000, 41, 203-208), subtractive cloning, differential display (DD) (Jurecic and Belmont, *Curr. Opin. Microbiol.*, 2000, 3, 316-21), comparative genomic hybridization (Carulli, et al., *J. Cell Biochem. Suppl.*, 1998, 31, 286-96), FISH (fluorescent in situ hybridization) techniques (Going and Gusterson, *Eur. J. Cancer*, 1999, 35, 1895-904) and mass spectrometry methods (To, *Comb. Chem. High Throughput Screen*, 2000, 3, 235-41).

[0080] The antisense compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding HIF1-beta and inhibit their function. The primers and probes disclosed herein are useful in methods requiring the specific detection of nucleic acid molecules encoding HIF1-beta and in the amplification of said nucleic acid molecules for detection or for use in further studies of HIF1-beta. Hybridization of the primers and probes with a nucleic acid encoding HIF1-beta can be detected by means known in the art. Such means may include conjugation of an enzyme to the primer or probe, radiolabeling of the primer or probe or any other suitable detection means. Kits using such detection means for detecting the level of HIF1-beta in a sample may also be prepared.

[0081] The specificity and sensitivity of antisense is also harnessed by those of skill in the art for therapeutic uses. Antisense compounds are employed as therapeutic moieties in the treatment of disease states in animals, including humans. Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway.

It is thus established that antisense compounds are useful therapeutic modalities that can be configured to be useful in treatment regimes for the treatment of cells, tissues and animals, especially humans.

[0082] For therapeutics, an animal, preferably a human, suspected of having a disease or disorder which can be treated by modulating the expression of HIF1-beta is treated by administering antisense compounds in accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to the animal in need of treatment, a therapeutically effective amount of a HIF1-beta inhibitor. The HIF1-beta inhibitors of the present invention effectively inhibit the activity of the HIF1-beta protein or inhibit the expression of the HIF1-beta protein. In one embodiment, the activity or expression of HIF1-beta in an animal is inhibited by about 10%. Preferably, the activity or expression of HIF1-beta in an animal is inhibited by about 25%. More preferably, the activity or expression of HIF1-beta in an animal is inhibited by 40% or more. Thus, the oligomeric antisense compounds modulate expression of HIF1-beta mRNA by at least 10%, by at least 20%, by at least 25%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 98%, by at least 99%, or by 100%.

[0083] For example, the reduction of the expression of HIF1-beta may be measured in serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal. Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding HIF1-beta protein and/or the HIF1-beta protein itself.

[0084] The antisense compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the compounds and methods of the invention may also be useful prophylactically.

E. Modifications

[0085] As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic base sometimes referred to as a "nucleobase" or simply a "base". The two most common classes of such heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to either the 2', 3' or 5' hydroxyl moiety of the sugar. In forming oligonucleotides, the phosphate groups covalently link adjacent nucleosides to one another to form a linear polymeric compound. In turn, the respective ends of this linear polymeric compound can be further joined to form a circular compound, however, linear compounds are generally preferred. In addition, linear compounds may have internal nucleobase complementarity and may therefore fold in a manner as to produce a fully or partially double-stranded compound. Within oligonucleotides, the phosphate groups are commonly referred to as forming the internucleoside backbone of the oligonucleotide. The normal linkage or backbone of RNA and DNA is a 3' to 5' phosphodiester linkage.

Modified Internucleoside Linkages (Backbones)

[0086] Specific examples of oligomeric antisense compounds useful in this invention include oligonucleotides con-

taining modified e.g. non-naturally occurring internucleoside linkages. As defined in this specification, oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom and internucleoside linkages that do not have a phosphorus atom. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides.

[0087] Oligomeric compounds of the invention can have one or more modified internucleoside linkages. One phosphorus-containing modified internucleoside linkage is the phosphorothioate internucleoside linkage. Other modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkyl-phosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkyl-phosphotriesters, phosphonoacetate and thiophosphonoacetate (see Sheehan et al., *Nucleic Acids Research*, 2003, 31(14), 4109-4118 and Dellinger et al., *J. Am. Chem. Soc.*, 2003, 125, 940-950), selenophosphates and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included.

[0088] N3'-P5'-phosphoramidates have been reported to exhibit both a high affinity towards a complementary RNA strand and nuclease resistance (Gryaznov et al., *J. Am. Chem. Soc.*, 1994, 116, 3143-3144). N3'-P5'-phosphoramidates have been studied with some success in vivo to specifically down regulate the expression of the c-myc gene (Skorski et al., *Proc. Natl. Acad. Sci.*, 1997, 94, 3966-3971; and Faira et al., *Nat. Biotechnol.*, 2001, 19, 40-44).

[0089] Representative United States patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 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; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, each of which is herein incorporated by reference.

[0090] In some embodiments of the invention, oligomeric compounds may have one or more phosphorothioate and/or heteroatom internucleoside linkages, in particular $\text{—CH}_2\text{—NH—O—CH}_2\text{—}$, $\text{—CH}_2\text{—N(CH}_3\text{)—O—CH}_2\text{—}$ (known as a methylene (methylimino) or MMI backbone), $\text{—CH}_2\text{—O—N(CH}_3\text{)—CH}_2\text{—}$, $\text{—CH}_2\text{—N(CH}_3\text{)—N(CH}_3\text{)—CH}_2\text{—}$ and $\text{—O—N(CH}_3\text{)—CH}_2\text{—CH}_2\text{—}$ (wherein the native phosphodiester internucleotide linkage is represented as $\text{—O—P(=O)(OH)—O—CH}_2\text{—}$). The MMI type internucleoside linkages are disclosed in the above referenced U.S. Pat. No. 5,489,677. Amide internucleoside linkages are disclosed in the above referenced U.S. Pat. No. 5,602,240.

[0091] Some oligonucleotide backbones that do not include a phosphorus atom therein 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 morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

[0092] Representative United States patents that teach 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; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, each of which is herein incorporated by reference.

Modified Sugar and Internucleoside Linkages (Mimetics)

[0093] Another group of oligomeric compounds amenable to the present invention includes oligonucleotide mimetics. The term mimetic as it is applied to oligonucleotides is intended to include oligomeric compounds wherein the furanose ring or the furanose ring and the internucleotide linkage are replaced with novel groups, replacement of only the furanose ring is also referred to in the art as being a sugar surrogate. The heterocyclic base moiety or a modified heterocyclic base moiety is maintained for hybridization with an appropriate target nucleic acid.

[0094] One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). Nielsen et al., *Science*, 1991, 254, 1497-1500. PNAs have favorable hybridization properties, high biological stability and are electrostatically neutral molecules. In one recent study PNA compounds were used to correct aberrant splicing in a transgenic mouse model (Sazani et al., *Nat. Biotechnol.*, 2002, 20, 1228-1233). In PNA oligomeric compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are bound directly or indirectly ($\text{—C(=O)—CH}_2\text{—}$ as shown below) to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA oligomeric compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. PNA compounds can be obtained commercially from Applied Biosystems (Foster City, Calif., USA). Numerous modifications to the basic PNA backbone are known in the art; particularly useful are PNA compounds with one or more amino acids conjugated to one or both termini. In particular, 1-8 lysine or arginine residues are useful when conjugated to the end of a PNA molecule.

[0095] Another class of oligonucleotide mimetic that has been studied is based on linked morpholino units (morpholino nucleic acid) having heterocyclic bases attached to the morpholino ring. A number of linking groups have been

reported that link the morpholino monomeric units in a morpholino nucleic acid. One class of linking groups have been selected to give a non-ionic oligomeric compound. The non-ionic morpholino-based oligomeric compounds are less likely to have undesired interactions with cellular proteins. Morpholino-based oligomeric compounds are non-ionic mimics of oligonucleotides which are less likely to form undesired interactions with cellular proteins (Dwayne A. Braasch and David R. Corey, *Biochemistry*, 2002, 41(14), 4503-4510). Morpholino-based oligomeric compounds have been studied in zebrafish embryos (see: *Genesis*, volume 30, issue 3, 2001 and Heasman, J., *Dev. Biol.*, 2002, 243, 209-214). Further studies of morpholino-based oligomeric compounds have also been reported (see: Nasevicius et al., *Nat. Genet.*, 2000, 26, 216-220; and Lacerra et al., *Proc. Natl. Acad. Sci.*, 2000, 97, 9591-9596). Morpholino-based oligomeric compounds are disclosed in U.S. Pat. No. 5,034,506, issued Jul. 23, 1991. The morpholino class of oligomeric compounds have been prepared having a variety of different linking groups joining the monomeric subunits. Linking groups can be varied from chiral to achiral, and from charged to neutral. U.S. Pat. No. 5,166,315 discloses linkages including $\text{—O—P(=O)(N(CH}_3)_2)\text{—O—}$; U.S. Pat. No. 5,034,506 discloses achiral intermorpholino linkages; and U.S. Pat. No. 5,185,444 discloses phosphorus containing chiral intermorpholino linkages.

[0096] A further class of oligonucleotide mimetic is referred to as cyclohexenyl nucleic acids (CeNA). The furanose ring normally present in a DNA or RNA molecule is replaced with a cyclohexenyl ring. CeNA DMT protected phosphoramidite monomers have been prepared and used for oligomeric compound synthesis following classical phosphoramidite chemistry. Fully modified CeNA oligomeric compounds and oligonucleotides having specific positions modified with CeNA have been prepared and studied (see Wang et al., *J. Am. Chem. Soc.*, 2000, 122, 8595-8602). In general the incorporation of CeNA monomers into a DNA chain increases its stability of a DNA/RNA hybrid. CeNA oligoadenylates formed complexes with RNA and DNA complements with similar stability to the native complexes. The study of incorporating CeNA structures into natural nucleic acid structures was shown by NMR and circular dichroism to proceed with easy conformational adaptation. Furthermore the incorporation of CeNA into a sequence targeting RNA was stable to serum and able to activate *E. coli* RNase resulting in cleavage of the target RNA strand.

[0097] A further modification includes bicyclic sugar moieties such as "Locked Nucleic Acids" (LNAs) in which the 2'-hydroxyl group of the ribosyl sugar ring is linked to the 4' carbon atom of the sugar ring thereby forming a 2'-C,4'-C-oxymethylene linkage to form the bicyclic sugar moiety (reviewed in Elayadi et al., *Curr. Opinion Invers. Drugs*, 2001, 2, 558-561; Braasch et al., *Chem. Biol.*, 2001, 8 1-7; and Orum et al., *Curr. Opinion Mol. Ther.*, 2001, 3, 239-243; see also U.S. Pat. Nos. 6,268,490 and 6,670,461). The linkage can be a methylene ($\text{—CH}_2\text{—}$) group bridging the 2' oxygen atom and the 4' carbon atom, for which the term LNA is used for the bicyclic moiety; in the case of an ethylene group in this position, the term ENATM is used (Singh et al., *Chem. Commun.*, 1998, 4, 455-456; ENATM: Morita et al., *Bioorganic Medicinal Chemistry*, 2003, 11, 2211-2226). LNA and other bicyclic sugar analogs display very high duplex thermal stabilities with complementary DNA and RNA (T_m =+3 to +10 C), stability towards 3'-exonucleolytic degradation and good

solubility properties. LNAs are commercially available from ProLigo (Paris, France and Boulder, Colo., USA).

[0098] An isomer of LNA that has also been studied is ∇ -L-LNA which has been shown to have superior stability against a 3'-exonuclease (Frieden et al., *Nucleic Acids Research*, 2003, 21, 6365-6372). The ∇ -L-LNA's were incorporated into antisense gapmers and chimeras that showed potent antisense activity.

[0099] Another similar bicyclic sugar moiety that has been prepared and studied has the bridge going from the 3'-hydroxyl group via a single methylene group to the 4' carbon atom of the sugar ring thereby forming a 3'-C,4'-C-oxymethylene linkage (see U.S. Pat. No. 6,043,060).

[0100] The conformations of LNAs determined by 2D NMR spectroscopy have shown that the locked orientation of the LNA nucleotides, both in single-stranded LNA and in duplexes, constrains the phosphate backbone in such a way as to introduce a higher population of the N-type conformation (Petersen et al., *J. Mol. Recognit.*, 2000, 13, 44-53). These conformations are associated with improved stacking of the nucleobases (Wengel et al., *Nucleosides Nucleotides*, 1999, 18, 1365-1370).

[0101] LNA has been shown to form exceedingly stable LNA:LNA duplexes (Koshkin et al., *J. Am. Chem. Soc.*, 1998, 120, 13252-13253). LNA:LNA hybridization was shown to be the most thermally stable nucleic acid type duplex system, and the RNA-mimicking character of LNA was established at the duplex level. Introduction of 3 LNA monomers (T or A) significantly increased melting points (T_m =+15/+11) toward DNA complements. The universality of LNA-mediated hybridization has been stressed by the formation of exceedingly stable LNA:LNA duplexes. The RNA-mimicking of LNA was reflected with regard to the N-type conformational restriction of the monomers and to the secondary structure of the LNA:RNA duplex.

[0102] LNAs also form duplexes with complementary DNA, RNA or LNA with high thermal affinities. Circular dichroism (CD) spectra show that duplexes involving fully modified LNA (esp. LNA:RNA) structurally resemble an A-form RNA:RNA duplex. Nuclear magnetic resonance (NMR) examination of an LNA:DNA duplex confirmed the 3'-endo conformation of an LNA monomer. Recognition of double-stranded DNA has also been demonstrated suggesting strand invasion by LNA. Studies of mismatched sequences show that LNAs obey the Watson-Crick base pairing rules with generally improved selectivity compared to the corresponding unmodified reference strands. DNA•LNA chimeras have been shown to efficiently inhibit gene expression when targeted to a variety of regions (5'-untranslated region, region of the start codon or coding region) within the luciferase mRNA (Braasch et al., *Nucleic Acids Research*, 2002, 30, 5160-5167).

[0103] Potent and nontoxic antisense oligonucleotides containing LNAs have been described (Wahlestedt et al., *Proc. Natl. Acad. Sci. U.S.A.*, 2000, 97, 5633-5638.) The authors have demonstrated that LNAs confer several desired properties to antisense agents. LNA/DNA copolymers were not degraded readily in blood serum and cell extracts. LNA/DNA copolymers exhibited potent antisense activity in assay systems as disparate as G-protein-coupled receptor signaling in living rat brain and detection of reporter genes in *Escherichia coli*. Lipofectin-mediated efficient delivery of LNA into living human breast cancer cells has also been accomplished. Further successful in vivo studies involving LNAs have

shown knock-down of the rat delta opioid receptor without toxicity (Wahlestedt et al., *Proc. Natl. Acad. Sci.*, 2000, 97, 5633-5638) and in another study showed a blockage of the translation of the large subunit of RNA polymerase II (Fluiter et al., *Nucleic Acids Res.*, 2003, 31, 953-962).

[0104] The synthesis and preparation of the LNA monomers adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin et al., *Tetrahedron*, 1998, 54, 3607-3630). LNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

[0105] The first analogs of LNA, phosphorothioate-LNA and 2'-thio-LNAs, have also been prepared (Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222). Preparation of locked nucleoside analogs containing oligodeoxyribo-nucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel et al., WO 99/14226). Furthermore, synthesis of 2'-amino-LNA, a novel conformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh et al., *J. Org. Chem.*, 1998, 63, 10035-10039). In addition, 2'-Amino- and 2'-methylamino-LNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

[0106] Another oligonucleotide mimetic amenable to the present invention that has been prepared and studied is threose nucleic acid. This oligonucleotide mimetic is based on threose nucleosides instead of ribose nucleosides. Initial interest in (3',2')- Ψ -L-threose nucleic acid (TNA) was directed to the question of whether a DNA polymerase existed that would copy the TNA. It was found that certain DNA polymerases are able to copy limited stretches of a TNA template (reported in C&EN/Jan. 13, 2003). In another study it was determined that TNA is capable of antiparallel Watson-Crick base pairing with complementary DNA, RNA and TNA oligonucleotides (Chaput et al., *J. Am. Chem. Soc.*, 2003, 125, 856-857).

[0107] In one study (3',2')- Ψ -L-threose nucleic acid was prepared and compared to the 2' and 3' amidate analogs (Wu et al., *Organic Letters*, 2002, 4(8), 1279-1282). The amidate analogs were shown to bind to RNA and DNA with comparable strength to that of RNA/DNA.

[0108] Further oligonucleotide mimetics have been prepared to include bicyclic and tricyclic nucleoside analogs (see Steffens et al., *Helv. Chim. Acta*, 1997, 80, 2426-2439; Steffens et al., *J. Am. Chem. Soc.*, 1999, 121, 3249-3255; Renneberg et al., *J. Am. Chem. Soc.*, 2002, 124, 5993-6002; and Renneberg et al., *Nucleic acids res.*, 2002, 30, 2751-2757). These modified nucleoside analogs have been oligomerized using the phosphoramidite approach and the resulting oligomeric compounds containing tricyclic nucleoside analogs have shown increased thermal stabilities (Tms) when hybridized to DNA, RNA and itself. Oligomeric compounds containing bicyclic nucleoside analogs have shown thermal stabilities approaching that of DNA duplexes.

[0109] Another class of oligonucleotide mimetic is referred to as phosphonomonoester nucleic acids which incorporate a phosphorus group in the backbone. This class of oligonucleotide mimetic is reported to have useful physical and biological and pharmacological properties in the areas of inhibiting gene expression (antisense oligonucleotides, ribozymes, sense oligonucleotides and triplex-forming oligonucleotides), as probes for the detection of nucleic acids and as

auxiliaries for use in molecular biology. Further oligonucleotide mimetics amenable to the present invention have been prepared wherein a cyclobutyl ring replaces the naturally occurring furanosyl ring.

Modified Sugars

[0110] Oligomeric compounds may also contain one or more substituted sugar moieties. Suitable compounds can comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Particularly suitable are O((CH₂)_nO)_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON((CH₂)_nCH₃)₂, where n and m are from 1 to about 10. Other oligonucleotides comprise one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, 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. One modification includes 2'-methoxyethoxy (2'-O—CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further modification includes 2'-dimethylaminoethoxyethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethyl-amino-ethoxy-ethyl or 2'-DMAEOE), i.e., 2'-O—CH₂—O—CH₂—N(CH₃)₂, also described in examples herein below.

[0111] Other modifications include 2'-methoxy(2'-O—CH₃), 2'-aminopropoxy(2'-OCH₂CH₂CH₂NH₂), 2'-allyl (2'-CH₂—CH=CH₂), 2'-O-allyl(2'-O—CH₂—CH=CH₂) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. One 2'-arabino modification is 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 and the 5' position of 5' terminal nucleotide. Antisense compounds may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures 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; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, each of which is herein incorporated by reference in its entirety.

[0112] In one aspect of the present invention oligomeric compounds include nucleosides synthetically modified to induce a 3'-endo sugar conformation. A nucleoside can incorporate synthetic modifications of the heterocyclic base, the sugar moiety or both to induce a desired 3'-endo sugar conformation. These modified nucleosides are used to mimic RNA like nucleosides so that particular properties of an oligomeric compound can be enhanced while maintaining the

desirable 3'-endo conformational geometry. There is an apparent preference for an RNA type duplex (A form helix, predominantly 3'-endo) as a requirement (e.g. trigger) of RNA interference which is supported in part by the fact that duplexes composed of 2'-deoxy-2'-F-nucleosides appears efficient in triggering RNAi response in the *C. elegans* system. Properties that are enhanced by using more stable 3'-endo nucleosides include but are not limited to: modulation of pharmacokinetic properties through modification of protein binding, protein off-rate, absorption and clearance; modulation of nuclease stability as well as chemical stability; modulation of the binding affinity and specificity of the oligomer (affinity and specificity for enzymes as well as for complementary sequences); and increasing efficacy of RNA cleavage. The present invention provides oligomeric triggers of RNAi having one or more nucleosides modified in such a way as to favor a C3'-endo type conformation.

[0113] Nucleoside conformation is influenced by various factors including substitution at the 2', 3' or 4'-positions of the pentofuranosyl sugar. Electronegative substituents generally prefer the axial positions, while sterically demanding substituents generally prefer the equatorial positions (Principles of Nucleic Acid Structure, Wolfgang Sanger, 1984, Springer-Verlag.) Modification of the 2' position to favor the 3'-endo conformation can be achieved while maintaining the 2'-OH as a recognition element, as illustrated in FIG. 2, below (Gallo et al., Tetrahedron (2001), 57, 5707-5713. Harry-O' kuru et al., J. Org. Chem., (1997), 62(6), 1754-1759 and Tang et al., J. Org. Chem. (1999), 64, 747-754.) Alternatively, preference for the 3'-endo conformation can be achieved by deletion of the 2'-OH as exemplified by 2' deoxy-2'F-nucleosides (Kawasaki et al., J. Med. Chem. (1993), 36, 831-841), which adopts the 3'-endo conformation positioning the electronegative fluorine atom in the axial position. Other modifications of the ribose ring, for example substitution at the 4'-position to give 4'-F modified nucleosides (Guillerm et al., Bioorganic and Medicinal Chemistry Letters (1995), 5, 1455-1460 and Owen et al., J. Org. Chem. (1976), 41, 3010-3017), or for example modification to yield methanocarba nucleoside analogs (Jacobson et al., J. Med. Chem. Lett. (2000), 43, 2196-2203 and Lee et al., Bioorganic and Medicinal Chemistry Letters (2001), 11, 1333-1337) also induce preference for the 3'-endo conformation. Along similar lines, oligomeric triggers of RNAi response might be composed of one or more nucleosides modified in such a way that conformation is locked into a C3'-endo type conformation, i.e. Locked Nucleic Acid (LNA, Singh et al, Chem. Commun. (1998), 4, 455-456), and ethylene bridged Nucleic Acids (ENA, Morita et al, Bioorganic & Medicinal Chemistry Letters (2002), 12, 73-76.)

[0114] One conformation of modified nucleosides and their oligomers can be estimated by various methods such as molecular dynamics calculations, nuclear magnetic resonance spectroscopy and CD measurements. Hence, modifications predicted to induce RNA like conformations, A-form duplex geometry in an oligomeric context, are selected for use in the modified oligonucleotides of the present invention. The synthesis of numerous of the modified nucleosides amenable to the present invention are known in the art (see for example, Chemistry of Nucleosides and Nucleotides Vol 1-3, ed. Leroy B. Townsend, 1988, Plenum press., and the examples section below.)

[0115] The terms used to describe the conformational geometry of homoduplex nucleic acids are "A Form" for

RNA and "B Form" for DNA. The respective conformational geometry for RNA and DNA duplexes was determined from X-ray diffraction analysis of nucleic acid fibers (Arnott and Hukins, *Biochem. Biophys. Res. Comm.*, 1970, 47, 1504.) In general, RNA:RNA duplexes are more stable and have higher melting temperatures (Tms) than DNA:DNA duplexes (Sanger et al., Principles of Nucleic Acid Structure, 1984, Springer-Verlag; New York, N.Y.; Lesnik et al., *Biochemistry*, 1995, 34, 10807-10815; Conte et al., *Nucleic Acids Res.*, 1997, 25, 2627-2634). The increased stability of RNA has been attributed to several structural features, most notably the improved base stacking interactions that result from an A-form geometry (Searle et al., *Nucleic Acids Res.*, 1993, 21, 2051-2056). The presence of the 2' hydroxyl in RNA biases the sugar toward a C3' endo pucker, i.e., also designated as Northern pucker, which causes the duplex to favor the A-form geometry. In addition, the 2' hydroxyl groups of RNA can form a network of water mediated hydrogen bonds that help stabilize the RNA duplex (Egli et al., *Biochemistry*, 1996, 35, 8489-8494). On the other hand, deoxy nucleic acids prefer a C2' endo sugar pucker, i.e., also known as Southern pucker, which is thought to impart a less stable B-form geometry (Sanger, W. (1984) Principles of Nucleic Acid Structure, Springer-Verlag, New York, N.Y.). As used herein, B-form geometry is inclusive of both C2'-endo pucker and O4'-endo pucker. This is consistent with Berger, et. al., *Nucleic Acids Research*, 1998, 26, 2473-2480, who pointed out that in considering the furanose conformations which give rise to B-form duplexes consideration should also be given to a O4'-endo pucker contribution. DNA:RNA hybrid duplexes, however, are usually less stable than pure RNA:RNA duplexes, and depending on their sequence may be either more or less stable than DNA:DNA duplexes (Searle et al., *Nucleic Acids Res.*, 1993, 21, 2051-2056). The structure of a hybrid duplex is intermediate between A- and B-form geometries, which may result in poor stacking interactions (Lane et al., *Eur. J. Biochem.*, 1993, 215, 297-306; Fedoroff et al., *J. Mol. Biol.*, 1993, 233, 509-523; Gonzalez et al., *Biochemistry*, 1995, 34, 4969-4982; Horton et al., *J. Mol. Biol.*, 1996, 264, 521-533). The stability of the duplex formed between a target RNA and a synthetic sequence is central to therapies such as but not limited to antisense and RNA interference as these mechanisms require the binding of a synthetic oligomer strand to an RNA target strand. In the case of antisense, effective inhibition of the mRNA requires that the antisense DNA have a very high binding affinity with the mRNA. Otherwise the desired interaction between the synthetic oligomer strand and target mRNA strand will occur infrequently, resulting in decreased efficacy.

[0116] One routinely used method of modifying the sugar pucker is the substitution of the sugar at the 2'-position with a substituent group that influences the sugar geometry. The influence on ring conformation is dependant on the nature of the substituent at the 2'-position. A number of different substituents have been studied to determine their sugar pucker effect. For example, 2'-halogens have been studied showing that the 2'-fluoro derivative exhibits the largest population (65%) of the C3'-endo form, and the 2'-iodo exhibits the lowest population (7%). The populations of adenosine (2'-OH) versus deoxyadenosine (2'-H) are 36% and 19%, respectively. Furthermore, the effect of the 2'-fluoro group of adenosine dimers (2'-deoxy-2'-fluoroadenosine-2'-deoxy-2'-fluoro-adenosine) is further correlated to the stabilization of the stacked conformation.

[0117] As expected, the relative duplex stability can be enhanced by replacement of 2'-OH groups with 2'-F groups thereby increasing the C3'-endo population. It is assumed that the highly polar nature of the 2'-F bond and the extreme preference for C3'-endo puckering may stabilize the stacked conformation in an A-form duplex. Data from UV hypochromicity, circular dichroism, and ¹HNMR also indicate that the degree of stacking decreases as the electronegativity of the halo substituent decreases. Furthermore, steric bulk at the 2'-position of the sugar moiety is better accommodated in an A-form duplex than a B-form duplex. Thus, a 2'-substituent on the 3'-terminus of a dinucleoside monophosphate is thought to exert a number of effects on the stacking conformation: steric repulsion, furanose puckering preference, electrostatic repulsion, hydrophobic attraction, and hydrogen bonding capabilities. These substituent effects are thought to be determined by the molecular size, electronegativity, and hydrophobicity of the substituent. Melting temperatures of complementary strands is also increased with the 2'-substituted adenosine diphosphates. It is not clear whether the 3'-endo preference of the conformation or the presence of the substituent is responsible for the increased binding. However, greater overlap of adjacent bases (stacking) can be achieved with the 3'-endo conformation.

[0118] Increasing the percentage of C3'-endo sugars in a modified oligonucleotide targeted to an RNA target strand should preorganize this strand for binding to RNA. Of the several sugar modifications that have been reported and studied in the literature, the incorporation of electronegative substituents such as 2'-fluoro or 2'-alkoxy shift the sugar conformation towards the 3' endo (northern) pucker conformation. This preorganizes an oligonucleotide that incorporates such modifications to have an A-form conformational geometry. This A-form conformation results in increased binding affinity of the oligonucleotide to a target RNA strand.

[0119] Representative 2'-substituent groups amenable to the present invention that give A-form conformational properties (3'-endo) to the resultant duplexes include 2'-O-alkyl, 2'-β-substituted alkyl and 2'-fluoro substituent groups. Suitable for the substituent groups are various alkyl and aryl ethers and thioethers, amines and monoalkyl and dialkyl substituted amines. It is further intended that multiple modifications can be made to one or more of the oligomeric compounds of the invention at multiple sites of one or more monomeric subunits (nucleosides are suitable) and or inter-nucleoside linkages to enhance properties such as but not limited to activity in a selected application.

Natural and Modified Nucleobases

[0120] Antisense compounds may also include nucleobase (often referred to in the art as heterocyclic base or 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, thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl ($\text{—C}\equiv\text{C—CH}_3$) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo,

8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine (1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',4:5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deaza-guanosine, 2-aminopyridine and 2-pyridone. Further nucleobases 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 Englisch 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 Lebleu, B., ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the compounds 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-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

[0121] Representative United States patents that teach 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; 5,645,985; 5,830,653; 5,763,588; 6,005,096; and 5,681,941, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference, and U.S. Pat. No. 5,750,692, which is commonly owned with the instant application and also herein incorporated by reference.

Conjugates

[0122] Another modification of the antisense compounds of the invention involves chemically linking to the antisense compound one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. These moieties or conjugates can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterol, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins,

rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake, distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application PCT/US92/09196, filed Oct. 23, 1992, and U.S. Pat. No. 6,287,860, the entire disclosure of which are incorporated herein by reference. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety. Antisense compounds of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodo-benzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in U.S. patent application Ser. No. 09/334,130 (filed Jun. 15, 1999) which is incorporated herein by reference in its entirety.

[0123] Representative United States patents that teach 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; 5,525,465; 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; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 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, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference.

[0124] Oligomeric compounds used in the compositions of the present invention can also be modified to have one or more stabilizing groups that are generally attached to one or both termini of oligomeric compounds to enhance properties such as for example nuclease stability. Included in stabilizing groups are cap structures. By "cap structure or terminal cap moiety" is meant chemical modifications, which have been incorporated at either terminus of oligonucleotides (see for example Wincott et al., WO 97/26270, incorporated by reference herein). These terminal modifications protect the oligomeric compounds having terminal nucleic acid molecules from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap) or at the 3'-terminus (3'-cap) or can be present on both termini. In non-limiting examples, the 5'-cap includes inverted abasic residue (moiety), 4',5'-methylene

nucleotide; 1-(beta-D-erythrofuransyl) nucleotide, 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety (for more details see Wincott et al., International PCT publication No. WO 97/26270, incorporated by reference herein).

[0125] Particularly preferred 3'-cap structures of the present invention include, for example 4',5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Tyer, 1993, Tetrahedron 49, 1925; incorporated by reference herein).

[0126] Further 3' and 5'-stabilizing groups that can be used to cap one or both ends of an oligomeric compound to impart nuclease stability include those disclosed in WO 03/004602 published on Jan. 16, 2003.

Chimeric Compounds

[0127] It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide.

[0128] The present invention also includes antisense compounds which are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. Chimeric antisense oligonucleotides are thus a form of antisense compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, increased stability and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide-mediated inhibition of gene expression. The cleavage of RNA:RNA hybrids can, in like fashion, be

accomplished through the actions of endoribonucleases, such as RNaseL which cleaves both cellular and viral RNA. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

[0129] Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Chimeric antisense compounds can be of several different types. These include a first type wherein the “gap” segment of linked nucleosides is positioned between 5' and 3' “wing” segments of linked nucleosides and a second “open end” type wherein the “gap” segment is located at either the 3' or the 5' terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as “gapmers” or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as “hemimers” or “wingmers”. Such compounds have also been referred to in the art as hybrids. In a gapmer that is 20 nucleotides in length, a gap or wing can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 nucleotides in length. In one embodiment, a 20-nucleotide gapmer is comprised of a gap 8 nucleotides in length, flanked on both the 5' and 3' sides by wings 6 nucleotides in length. In another embodiment, a 20-nucleotide gapmer is comprised of a gap 10 nucleotides in length, flanked on both the 5' and 3' sides by wings 5 nucleotides in length. In another embodiment, a 20-nucleotide gapmer is comprised of a gap 12 nucleotides in length flanked on both the 5' and 3' sides by wings 4 nucleotides in length. In a further embodiment, a 20-nucleotide gapmer is comprised of a gap 14 nucleotides in length flanked on both the 5' and 3' sides by wings 3 nucleotides in length. In another embodiment, a 20-nucleotide gapmer is comprised of a gap 16 nucleotides in length flanked on both the 5' and 3' sides by wings 2 nucleotides in length. In a further embodiment, a 20-nucleotide gapmer is comprised of a gap 18 nucleotides in length flanked on both the 5' and 3' ends by wings 1 nucleotide in length. Alternatively, the wings are of different lengths, for example, a 20-nucleotide gapmer may be comprised of a gap 10 nucleotides in length, flanked by a 6-nucleotide wing on one side (5' or 3') and a 4-nucleotide wing on the other side (5' or 3').

[0130] In a hemimer, an “open end” chimeric antisense compound, 20 nucleotides in length, a gap segment, located at either the 5' or 3' terminus of the oligomeric compound, can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 nucleotides in length. For example, a 20-nucleotide hemimer can have a gap segment of 10 nucleotides at the 5' end and a second segment of 10 nucleotides at the 3' end. Alternatively, a 20-nucleotide hemimer can have a gap segment of 10 nucleotides at the 3' end and a second segment of 10 nucleotides at the 5' end.

[0131] Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

F. Formulations

[0132] The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated

with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor-targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption-assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

[0133] The antisense compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents.

[0134] The term “prodrug” indicates a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions. In particular, prodrug versions of the oligonucleotides of the invention are prepared as SATE [(S-acetyl-2-thioethyl) phosphate] derivatives according to the methods disclosed in WO 93/24510 to Gosselin et al., published Dec. 9, 1993 or in WO 94/26764 and U.S. Pat. No. 5,770,713 to Imbach et al.

[0135] The term “pharmaceutically acceptable salts” refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. For oligonucleotides, preferred examples of pharmaceutically acceptable salts and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0136] The present invention also includes pharmaceutical compositions and formulations which include the antisense compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

[0137] The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0138] The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

[0139] Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, foams and liposome-containing formulations. The pharmaceutical compositions and formulations of the present invention may comprise one or more penetration enhancers, carriers, excipients or other active or inactive ingredients.

[0140] The pharmaceutical formulations and compositions of the present invention may also include surfactants. The use of surfactants in drug products, formulations and in emulsions is well known in the art. Surfactants and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0141] In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly oligonucleotides. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Penetration enhancers and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0142] One of skill in the art will recognize that formulations are routinely designed according to their intended use, i.e. route of administration.

[0143] In another related embodiment, compositions of the invention may contain one or more antisense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional antisense compounds targeted to a second nucleic acid target. Alternatively, compositions of the invention may contain two or more antisense compounds targeted to different regions of the same nucleic acid target. Numerous examples of antisense compounds are known in the art. Two or more combined compounds may be used together or sequentially.

G. Dosing

[0144] The formulation of therapeutic compositions and their subsequent administration (dosing) is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of

the disease state is achieved. Such considerations are well known to those skilled in the art.

[0145] While the present invention has been described with specificity in accordance with certain of its preferred embodiments, the following examples serve only to illustrate the invention and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

EXAMPLES

Example 1

Synthesis of Nucleoside Phosphoramidites

[0146] The following compounds, including amidites and their intermediates were prepared as described in U.S. Pat. No. 6,426,220 and published PCT WO 02/36743; 5'- β -Dimethoxytrityl-thymidine intermediate for 5-methyl dC amidite, 5'-O-Dimethoxytrityl-2'-deoxy-5-methylcytidine intermediate for 5-methyl-dC amidite, 5'-O-Dimethoxytrityl-2'-deoxy-N⁴-benzoyl-5-methylcytidine penultimate intermediate for 5-methyl dC amidite, [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-deoxy-N⁴-benzoyl-5-methylcytidin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (5-methyl dC amidite), 2'-Fluorodeoxyadenosine, 2'-Fluorodeoxyguanosine, 2'-Fluorouridine, 2'-Fluorodeoxycytidine, 2'-O-(2-Methoxyethyl) modified amidites, 2'-O-(2-methoxyethyl)-5-methyluridine intermediate, 5'-O-DMT-2'-O-(2-methoxyethyl)-5-methyluridine penultimate intermediate, [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-5-methyluridin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE T amidite), 5'-O-Dimethoxytrityl-2'-O-(2-methoxyethyl)-5-methylcytidine intermediate, 5'-O-dimethoxytrityl-2'-O-(2-methoxyethyl)-N⁴-benzoyl-5-methyl-cytidine penultimate intermediate, [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N⁴-benzoyl-5-methylcytidin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE 5-Me-C amidite), [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N⁶-benzoyladenoin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE A amidite), [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxyethyl)-N⁴-isobutyrylguanosin-3'-O-yl]-2-cyanoethyl-N,N-diisopropylphosphoramidite (MOE G amidite), 2'-O-(Aminooxyethyl) nucleoside amidites and 2'-O-(dimethylaminoxy-ethyl) nucleoside amidites, 2'-(Dimethylaminoxyethoxy) nucleoside amidites, 5'-O-tert-Butyldiphenylsilyl-O²-2'-anhydro-5-methyluridine, 5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine, 2'-O-([2-phthalimidoxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine, 5'-O-tert-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy)ethyl]-5-methyluridine, 5'-O-tert-Butyldiphenylsilyl-2'-O-[N,N-dimethylaminoxyethyl]-5-methyluridine, 2'-O-(dimethylaminoxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(dimethylaminoxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(2-N,N-dimethylaminoxyethyl)-5-methyluridine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite], 2'-(Aminooxyethoxy) nucleoside amidites, N²-isobutyryl-6-O-diphenylcarbamoyle-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite], 2'-dimethylaminoethoxyethoxy(2'-DMAEOE) nucleoside amidites, 2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl]-5-

methyl uridine, 5'-O-dimethoxytrityl-2'-O-[2(2-N,N-dimethyl-aminoethoxy)-ethyl]-5-methyl uridine and 5'-O-Dimethoxytrityl-2'-O-[2(2-N,N-dimethylaminoethoxy)-ethyl]-5-methyl uridine-3'-O-(cyanoethyl-N,N-diisopropyl) phosphoramidite.

Example 2

Oligonucleotide and Oligonucleoside Synthesis

[0147] The antisense compounds used in accordance with this 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 well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives.

Oligonucleotides

[0148] Unsubstituted and substituted phosphodiester (P=O) oligonucleotides are synthesized on an automated DNA synthesizer (Applied Biosystems model 394) using standard phosphoramidite chemistry with oxidation by iodine.

[0149] Phosphorothioates (P=S) are synthesized similar to phosphodiester oligonucleotides with the following exceptions: thiation was effected by utilizing a 10% w/v solution of 3,4-dihydro-2-benzodithiole-3-one 1,1-dioxide in acetonitrile for the oxidation of the phosphite linkages. The thiation reaction step time was increased to 180 sec and preceded by the normal capping step. After cleavage from the CPG column and deblocking in concentrated ammonium hydroxide at 55° C. (12-16 hr), the oligonucleotides were recovered by precipitating with >3 volumes of ethanol from a 1 M NH₄OAc solution. Phosphinate oligonucleotides are prepared as described in U.S. Pat. No. 5,508,270, herein incorporated by reference.

[0150] Alkyl phosphonate oligonucleotides are prepared as described in U.S. Pat. No. 4,469,863, herein incorporated by reference.

[0151] 3'-Deoxy-3'-methylene phosphonate oligonucleotides are prepared as described in U.S. Pat. No. 5,610,289 or 5,625,050, herein incorporated by reference.

[0152] Phosphoramidite oligonucleotides are prepared as described in U.S. Pat. No. 5,256,775 or U.S. Pat. No. 5,366,878, herein incorporated by reference.

[0153] Alkylphosphonothioate oligonucleotides are prepared as described in published PCT applications PCT/US94/00902 and PCT/US93/06976 (published as WO 94/17093 and WO 94/02499, respectively), herein incorporated by reference.

[0154] 3'-Deoxy-3'-amino phosphoramidate oligonucleotides are prepared as described in U.S. Pat. No. 5,476,925, herein incorporated by reference.

[0155] Phosphotriester oligonucleotides are prepared as described in U.S. Pat. No. 5,023,243, herein incorporated by reference.

[0156] Borano phosphate oligonucleotides are prepared as described in U.S. Pat. Nos. 5,130,302 and 5,177,198, both herein incorporated by reference.

Oligonucleosides

[0157] Methylenemethylimino linked oligonucleosides, also identified as MMI linked oligonucleosides, methylene-

dimethylhydrazo linked oligonucleosides, also identified as MDH linked oligonucleosides, and methylenecarbonylamino linked oligonucleosides, also identified as amide-3 linked oligonucleosides, and methyleneaminocarbonyl linked oligonucleosides, also identified as amide-4 linked oligonucleosides, as well as mixed backbone compounds having, for instance, alternating MMI and P=O or P=S linkages are prepared as described in U.S. Pat. Nos. 5,378,825, 5,386,023, 5,489,677, 5,602,240 and 5,610,289, all of which are herein incorporated by reference.

[0158] Formacetal and thioformacetal linked oligonucleosides are prepared as described in U.S. Pat. Nos. 5,264,562 and 5,264,564, herein incorporated by reference.

[0159] Ethylene oxide linked oligonucleosides are prepared as described in U.S. Pat. No. 5,223,618, herein incorporated by reference.

Example 3

RNA Synthesis

[0160] In general, RNA synthesis chemistry is based on the selective incorporation of various protecting groups at strategic intermediary reactions. Although one of ordinary skill in the art will understand the use of protecting groups in organic synthesis, a useful class of protecting groups includes silyl ethers. In particular bulky silyl ethers are used to protect the 5'-hydroxyl in combination with an acid-labile orthoester protecting group on the 2'-hydroxyl. This set of protecting groups is then used with standard solid-phase synthesis technology. It is important to lastly remove the acid labile orthoester protecting group after all other synthetic steps. Moreover, the early use of the silyl protecting groups during synthesis ensures facile removal when desired, without undesired deprotection of 2' hydroxyl.

[0161] Following this procedure for the sequential protection of the 5'-hydroxyl in combination with protection of the 2'-hydroxyl by protecting groups that are differentially removed and are differentially chemically labile, RNA oligonucleotides were synthesized.

[0162] RNA oligonucleotides are synthesized in a stepwise fashion. Each nucleotide is added sequentially (3'- to 5'-direction) to a solid support-bound oligonucleotide. The first nucleoside at the 3'-end of the chain is covalently attached to a solid support. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are added, coupling the second base onto the 5'-end of the first nucleoside. The support is washed and any unreacted 5'-hydroxyl groups are capped with acetic anhydride to yield 5'-acetyl moieties. The linkage is then oxidized to the more stable and ultimately desired P(V) linkage. At the end of the nucleotide addition cycle, the 5'-silyl group is cleaved with fluoride. The cycle is repeated for each subsequent nucleotide.

[0163] Following synthesis, the methyl protecting groups on the phosphates are cleaved in 30 minutes utilizing 1 M disodium-2-carbamoyl-2-cyanoethylene-1,1-dithiolate trihydrate (S₂Na₂) in DMF. The deprotection solution is washed from the solid support-bound oligonucleotide using water. The support is then treated with 40% methylamine in water for 10 minutes at 55° C. This releases the RNA oligonucleotides into solution, deprotects the exocyclic amines, and modifies the 2'-groups. The oligonucleotides can be analyzed by anion exchange HPLC at this stage.

[0164] The 2'-orthoester groups are the last protecting groups to be removed. The ethylene glycol monoacetate

orthoester protecting group developed by Dharmacon Research, Inc. (Lafayette, Colo.), is one example of a useful orthoester protecting group which, has the following important properties. It is stable to the conditions of nucleoside phosphoramidite synthesis and oligonucleotide synthesis. However, after oligonucleotide synthesis the oligonucleotide is treated with methylamine which not only cleaves the oligonucleotide from the solid support but also removes the acetyl groups from the orthoesters. The resulting 2-ethyl-hydroxyl substituents on the orthoester are less electron withdrawing than the acetylated precursor. As a result, the modified orthoester becomes more labile to acid-catalyzed hydrolysis. Specifically, the rate of cleavage is approximately 10 times faster after the acetyl groups are removed. Therefore, this orthoester possesses sufficient stability in order to be compatible with oligonucleotide synthesis and yet, when subsequently modified, permits deprotection to be carried out under relatively mild aqueous conditions compatible with the final RNA oligonucleotide product.

[0165] Additionally, methods of RNA synthesis are well known in the art (Scaringe, S. A. Ph.D. Thesis, University of Colorado, 1996; Scaringe, S. A., et al., *J. Am. Chem. Soc.*, 1998, 120, 11820-11821; Matteucci, M. D. and Caruthers, M. H. *J. Am. Chem. Soc.*, 1981, 103, 3185-3191; Beaucage, S. L. and Caruthers, M. H. *Tetrahedron Lett.*, 1981, 22, 1859-1862; Dahl, B. J., et al., *Acta Chem. Scand.*, 1990, 44, 639-641; Reddy, M. P., et al., *Tetrahedron Lett.*, 1994, 25, 4311-4314; Wincott, F. et al., *Nucleic Acids Res.*, 1995, 23, 2677-2684; Griffin, B. E., et al., *Tetrahedron*, 1967, 23, 2301-2313; Griffin, B. E., et al., *Tetrahedron*, 1967, 23, 2315-2331).

[0166] RNA antisense compounds (RNA oligonucleotides) of the present invention can be synthesized by the methods herein or purchased from Dharmacon Research, Inc (Lafayette, Colo.). Once synthesized, complementary RNA antisense compounds can then be annealed by methods known in the art to form double stranded (duplexed) antisense compounds. For example, duplexes can be formed by combining 30 μ l of each of the complementary strands of RNA oligonucleotides (50 μ M RNA oligonucleotide solution) and 15 μ l of 5 $\times$ annealing buffer (100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, 2 mM magnesium acetate) followed by heating for 1 minute at 90° C., then 1 hour at 37° C. The resulting duplexed antisense compounds can be used in kits, assays, screens, or other methods to investigate the role of a target nucleic acid, or for diagnostic or therapeutic purposes.

Example 4

Synthesis of Chimeric Compounds

[0167] Chimeric oligonucleotides, oligonucleosides or mixed oligonucleotides/oligonucleosides of the invention can be of several different types. These include a first type wherein the "gap" segment of linked nucleosides is positioned between 5' and 3' "wing" segments of linked nucleosides and a second "open end" type wherein the "gap" segment is located at either the 3' or the 5' terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as "gapmers" or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as "hemimers" or "wingmers".

[2'-O-Me]-[2'-deoxy]-[2'-O-Me] Chimeric Phosphorothioate Oligonucleotides

[0168] Chimeric oligonucleotides having 2'-O-alkyl phosphorothioate and 2'-deoxy phosphorothioate oligonucleotide

segments are synthesized using an Applied Biosystems automated DNA synthesizer Model 394, as above. Oligonucleotides are synthesized using the automated synthesizer and 2'-deoxy-5'-dimethoxytrityl-3'-O-phosphoramidite for the DNA portion and 5'-dimethoxytrityl-2'-O-methyl-3'-O-phosphoramidite for 5' and 3' wings. The standard synthesis cycle is modified by incorporating coupling steps with increased reaction times for the 5'-dimethoxytrityl-2'-O-methyl-3'-O-phosphoramidite. The fully protected oligonucleotide is cleaved from the support and deprotected in concentrated ammonia (NH₄OH) for 12-16 hr at 55° C. The deprotected oligo is then recovered by an appropriate method (precipitation, column chromatography, volume reduced in vacuo and analyzed spectrophotometrically for yield and for purity by capillary electrophoresis and by mass spectrometry.

[2'-O-(2-Methoxyethyl)]-[2'-deoxy]-[2'-O-(Methoxyethyl)] Chimeric Phosphorothioate Oligonucleotides

[0169] [2'-O-(2-methoxyethyl)]-[2'-deoxy]-[2'-O-(methoxyethyl)] chimeric phosphorothioate oligonucleotides were prepared as per the procedure above for the 2'-O-methyl chimeric oligonucleotide, with the substitution of 2'-O-(methoxyethyl) amidites for the 2'-O-methyl amidites.

[2'-O-(2-Methoxyethyl)Phosphodiester]-[2'-deoxy Phosphorothioate]-[2'-O-(2-Methoxyethyl) Phosphodiester] Chimeric Oligonucleotides

[0170] [2'-O-(2-methoxyethyl phosphodiester)-[2'-deoxy phosphorothioate]-[2'-O-(methoxyethyl) phosphodiester] chimeric oligonucleotides are prepared as per the above procedure for the 2'-O-methyl chimeric oligonucleotide with the substitution of 2'-O-(methoxyethyl)amidites for the 2'-O-methyl amidites, oxidation with iodine to generate the phosphodiester internucleotide linkages within the wing portions of the chimeric structures and sulfurization utilizing 3,4-dihydro-2H-benzothiole-3-one 1,1 dioxide (Beaucage Reagent) to generate the phosphorothioate internucleotide linkages for the center gap.

[0171] Other chimeric oligonucleotides, chimeric oligonucleosides and mixed chimeric oligonucleotides/oligonucleosides are synthesized according to U.S. Pat. No. 5,623, 065, herein incorporated by reference.

Example 5

Design and Screening of Duplexed Antisense Compounds Targeting HIF1-Beta

[0172] In accordance with the present invention, a series of nucleic acid duplexes comprising the antisense compounds of the present invention and their complements can be designed to target HIF1-beta. The nucleobase sequence of the antisense strand of the duplex comprises at least an 8-nucleobase portion of an oligonucleotide in Table 1 or Table 2. The ends of the strands may be modified by the addition of one or more natural or modified nucleobases to form an overhang. The sense strand of the dsRNA is then designed and synthesized as the complement of the antisense strand and may also contain modifications or additions to either terminus. For example, in one embodiment, both strands of the dsRNA duplex would be complementary over the central nucleobases, each having overhangs at one or both termini. The antisense and sense strands of the duplex comprise from about 17 to 25 nucleotides, or from about 19 to 23 nucle-

otides. Alternatively, the antisense and sense strands comprise 20, 21 or 22 nucleotides.

[0173] For example, a duplex comprising an antisense strand having the sequence CGAGAGGCGGACGGGACCG (SEQ ID NO: 187) and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

```

cgagaggcgggacgggaccgTT  Antisense Strand
|||||                      (SEQ ID NO: 188)
TTgctctccgctgcctggc     Sense Strand
                           (SEQ ID NO: 189)

```

[0174] Overhangs can range from 2 to 6 nucleobases and these nucleobases may or may not be complementary to the target nucleic acid. In another embodiment, the duplexes may have an overhang on only one terminus.

[0175] In another embodiment, a duplex comprising an antisense strand having the same sequence CGAGAGGCGGACGGGACCG may be prepared with blunt ends (no single stranded overhang) as shown:

```

cgagaggcgggacgggaccg  Antisense Strand
|||||                  (SEQ ID NO: 187)
gctctccgctgcctggc     Sense Strand
                        (SEQ ID NO: 190)

```

[0176] The RNA duplex can be unimolecular or bimolecular; i.e., the two strands can be part of a single molecule or may be separate molecules.

[0177] RNA strands of the duplex can be synthesized by methods disclosed herein or purchased from Dharmacon Research Inc., (Lafayette, Colo.). Once synthesized, the complementary strands are annealed. The single strands are aliquotted and diluted to a concentration of 50 μ M. Once diluted, 30 μ L of each strand is combined with 15 μ L of a 5 $\times$ solution of annealing buffer. The final concentration of said buffer is 100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, and 2 mM magnesium acetate. The final volume is 75 μ L. This solution is incubated for 1 minute at 90° C. and then centrifuged for 15 seconds. The tube is allowed to sit for 1 hour at 37° C. at which time the dsRNA duplexes are used in experimentation. The final concentration of the dsRNA duplex is 20 μ M. This solution can be stored frozen (−20° C.) and freeze-thawed up to 5 times.

[0178] Once prepared, the duplexed antisense compounds are evaluated for their ability to modulate HIF1-beta expression.

[0179] When cells reach 80% confluency, they are treated with duplexed antisense compounds of the invention. For cells grown in 96-well plates, wells are washed once with 200 μ L OPTI-MEM-1 reduced-serum medium (Gibco BRL) and then treated with 130 μ L of OPTI-MEM-1 containing 12 μ g/mL LIPOFECTIN (Gibco BRL) and the desired duplex antisense compound at a final concentration of 200 nM. After 5 hours of treatment, the medium is replaced with fresh medium. Cells are harvested 16 hours after treatment, at which time RNA is isolated and target reduction measured by RT-PCR.

Example 6

Oligonucleotide Isolation

[0180] After cleavage from the controlled pore glass solid support and deblocking in concentrated ammonium hydrox-

ide at 55° C. for 12-16 hours, the oligonucleotides or oligonucleosides are recovered by precipitation out of 1 M NH_4OAc with >3 volumes of ethanol. Synthesized oligonucleotides were analyzed by electrospray mass spectroscopy (molecular weight determination) and by capillary gel electrophoresis and judged to be at least 70% full length material. The relative amounts of phosphorothioate and phosphodiester linkages obtained in the synthesis was determined by the ratio of correct molecular weight relative to the −16 amu product (+/−32+/−48). For some studies oligonucleotides were purified by HPLC, as described by Chiang et al., *J. Biol. Chem.* 1991, 266, 18162-18171. Results obtained with HPLC-purified material were similar to those obtained with non-HPLC purified material.

Example 7

Oligonucleotide Synthesis—96 Well Plate Format

[0181] Oligonucleotides were synthesized via solid phase P(III) phosphoramidite chemistry on an automated synthesizer capable of assembling 96 sequences simultaneously in a 96-well format. Phosphodiester internucleotide linkages were afforded by oxidation with aqueous iodine. Phosphorothioate internucleotide linkages were generated by sulfuration utilizing 3,4-dihydro-2H-benzothiole-3-one 1,1 dioxide (Beaucage Reagent) in anhydrous acetonitrile. Standard base-protected beta-cyanoethyl-diisopropyl phosphoramidites were purchased from commercial vendors (e.g. PE-Applied Biosystems, Foster City, Calif., or Pharmacia, Piscataway, N.J.). Non-standard nucleosides are synthesized as per standard or patented methods. They are utilized as base protected beta-cyanoethyl-diisopropyl phosphoramidites.

[0182] Oligonucleotides were cleaved from support and deprotected with concentrated NH_4OH at elevated temperature (55-60° C.) for 12-16 hours and the released product then dried in vacuo. The dried product was then re-suspended in sterile water to afford a master plate from which all analytical and test plate samples are then diluted utilizing robotic pipettors.

Example 8

Oligonucleotide Analysis—96-Well Plate Format

[0183] The concentration of oligonucleotide in each well was assessed by dilution of samples and UV absorption spectroscopy. The full-length integrity of the individual products was evaluated by capillary electrophoresis (CE) in either the 96-well format (Beckman P/ACE™ MDQ) or, for individually prepared samples, on a commercial CE apparatus (e.g., Beckman P/ACE™ 5000, ABI 270). Base and backbone composition was confirmed by mass analysis of the compounds utilizing electrospray-mass spectroscopy. All assay test plates were diluted from the master plate using single and multi-channel robotic pipettors. Plates were judged to be acceptable if at least 85% of the compounds on the plate were at least 85% full length.

Example 9

Cell Culture and Oligonucleotide Treatment

[0184] The effect of antisense compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the target nucleic acid is present at measurable levels. This can be routinely determined using, for example,

PCR or Northern blot analysis. The following cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen. This can be readily determined by methods routine in the art, for example Northern blot analysis, ribonuclease protection assays, or RT-PCR.

[0185] T-24 Cells:

[0186] The human transitional cell bladder carcinoma cell line T-24 was obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). T-24 cells were routinely cultured in complete McCoy's 5A basal media (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, Calif.), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #353872) at a density of 7000 cells/well for use in RT-PCR analysis.

[0187] A549 Cells:

[0188] The human lung carcinoma cell line A549 was obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). A549 cells were routinely cultured in DMEM basal media (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, Calif.), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence.

[0189] NHDF Cells:

[0190] Human neonatal dermal fibroblast (NHDF) were obtained from the Clonetics Corporation (Walkersville, Md.). NHDFs were routinely maintained in Fibroblast Growth Medium (Clonetics Corporation, Walkersville, Md.) supplemented as recommended by the supplier. Cells were maintained for up to 10 passages as recommended by the supplier.

[0191] HEK Cells:

[0192] Human embryonic keratinocytes (HEK) were obtained from the Clonetics Corporation (Walkersville, Md.). HEKs were routinely maintained in Keratinocyte Growth Medium (Clonetics Corporation, Walkersville, Md.) formulated as recommended by the supplier. Cells were routinely maintained for up to 10 passages as recommended by the supplier.

[0193] b.END Cells:

[0194] The mouse brain endothelial cell line b.END was obtained from Dr. Werner Risau at the Max Plank Institute (Bad Nauheim, Germany). b.END cells were routinely cultured in DMEM, high glucose (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 3000 cells/well for use in RT-PCR analysis.

[0195] MCF7 Cells:

[0196] The human breast carcinoma cell line MCF-7 was obtained from the American Type Culture Collection (Manassas, Va.). MCF-7 cells were routinely cultured in DMEM low glucose supplemented with 10% fetal bovine serum (Invitrogen Life Technologies, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into poly-D-lysine coated

96-well plates (Falcon-Primaria #3872) at a density of 8000 cells/well for use in antisense oligonucleotide transfection.

[0197] PC3 Cells:

[0198] The human prostatic carcinoma cell line PC3 was obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). PC3 cells were routinely cultured in Ham's F12K medium with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate supplemented with 10% fetal bovine serum (Invitrogen Life Technologies, Carlsbad, Calif.) and antibiotics (Invitrogen Life Technologies, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached approximately 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #353872) at a density of approximately 6000 cells/well for use in antisense oligonucleotide transfection.

[0199] Hep3B Cells:

[0200] The human hepatoma cell line Hep3B (Hep3B2.1-7) was obtained from the American Type Culture Collection (ATCC-ATCC Catalog # HB-8064) (Manassas, Va.). This cell line was initially derived from a hepatocellular carcinoma of an 8-yr-old black male. The cells are epithelial in morphology and are tumorigenic in nude mice. Hep3B cells are routinely cultured in Minimum Essential Medium (MEM) with Earle's Balanced Salt Solution, 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 0.1 mM nonessential amino acids, 1.0 mM sodium pyruvate (ATCC #20-2003, Manassas, Va.) and with 10% heat-inactivated fetal bovine serum (Invitrogen Life Technologies, Carlsbad, Calif.). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence.

[0201] HeLa Cells:

[0202] The human epithelioid carcinoma cell line HeLa was obtained from the American Tissue Type Culture Collection (Manassas, Va.). HeLa cells were routinely cultured in DMEM, high glucose (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 24-well plates (Falcon-Primaria #3846) at a density of 50,000 cells/well or in 96-well plates at a density of 5,000 cells/well for use in RT-PCR analysis. For Northern blotting or other analyses, cells were harvested when they reached 90% confluence.

[0203] HuVEC Cells:

[0204] The human umbilical vein endothelial cell line HuVEC is obtained from Cascade Biologics (Portland, Oreg.). HuVEC cells are routinely cultured in EBM (Clonetics Corporation Walkersville, Md.) supplemented with SingleQuots supplements (Clonetics Corporation, Walkersville, Md.). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence and are maintained for up to 15 passages.

[0205] Treatment with Antisense Compounds:

[0206] When cells reached 65-75% confluency, they were treated with oligonucleotide. For cells grown in 96-well plates, wells were washed once with 100 μ L OPTI-MEM™-1 reduced-serum medium (Invitrogen Corporation, Carlsbad, Calif.) and then treated with 130 μ L of OPTI-MEM™-1 containing 3.75 μ g/mL LIPOFECTINT™ (Invitrogen Corporation, Carlsbad, Calif.) and the desired concentration of oligonucleotide. Cells are treated and data are obtained in triplicate. After 4-7 hours of treatment at 37° C., the medium was replaced with fresh medium. Cells were harvested 16-24 hours after oligonucleotide treatment.

[0207] The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control oligonucleotide is selected from either ISIS 13920 (TCCGT-CATCGCTCCTCAGGG, SEQ ID NO: 1) which is targeted to human H-ras, or ISIS 18078, (GTGCGCGCGAGC-CCGAAATC, SEQ ID NO: 2) which is targeted to human Jun-N-terminal kinase-2 (JNK2). Both controls are 2'-O-methoxyethyl gapmers (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone. For mouse or rat cells the positive control oligonucleotide is ISIS 15770 (ATGCA-TTCTGCCCCCAAGGA, SEQ ID NO: 3), a 2'- β -methoxyethyl gapmer (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to both mouse and rat c-raf. The concentration of positive control oligonucleotide that results in 80% inhibition of c-H-ras (for ISIS 13920), JNK2 (for ISIS 18078) or c-raf (for ISIS 15770) mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of c-H-ras, JNK2 or c-raf mRNA is then utilized as the oligonucleotide screening concentration in subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments. The concentrations of antisense oligonucleotides used herein are from 50 nM to 300 nM.

[0208] For Northern blotting or other analyses, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

Example 10

Analysis of Oligonucleotide Inhibition of HIF1-Beta Expression

[0209] Antisense modulation of HIF1-beta expression can be assayed in a variety of ways known in the art. For example, HIF1-beta mRNA levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or real-time PCR (RT-PCR). Real-time quantitative PCR is presently preferred. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. The preferred method of RNA analysis of the present invention is the use of total cellular RNA as described in other examples herein. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Real-time quantitative (PCR) can be conveniently accomplished using the commercially available ABI PRISM™ 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, Calif. and used according to manufacturer's instructions.

[0210] Protein levels of HIF1-beta can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA) or fluorescence-activated cell sorting (FACS). Antibodies directed to HIF1-beta can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Bir-

mingham, Mich.), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art.

Example 11

Design of Phenotypic Assays for the Use of HIF1-Beta Inhibitors

Phenotypic Assays

[0211] Once HIF1-beta inhibitors have been identified by the methods disclosed herein, the compounds are further investigated in one or more phenotypic assays, each having measurable endpoints predictive of efficacy in the treatment of a particular disease state or condition.

[0212] Phenotypic assays, kits and reagents for their use are well known to those skilled in the art and are herein used to investigate the role and/or association of HIF1-beta in health and disease. Representative phenotypic assays, which can be purchased from any one of several commercial vendors, include those for determining cell viability, cytotoxicity, proliferation or cell survival (Molecular Probes, Eugene, Oreg.; PerkinElmer, Boston, Mass.), protein-based assays including enzymatic assays (Panvera, LLC, Madison, Wis.; BD Biosciences, Franklin Lakes, N.J.; Oncogene Research Products, San Diego, Calif.), cell regulation, signal transduction, inflammation, oxidative processes and apoptosis (Assay Designs Inc., Ann Arbor, Mich.), triglyceride accumulation (Sigma-Aldrich, St. Louis, Mo.), angiogenesis assays, tube formation assays, cytokine and hormone assays and metabolic assays (Chemicon International Inc., Temecula, Calif.; Amersham Biosciences, Piscataway, N.J.).

[0213] In one non-limiting example, cells determined to be appropriate for a particular phenotypic assay (i.e., MCF-7 cells selected for breast cancer studies; adipocytes for obesity studies) are treated with HIF1-beta inhibitors identified from the in vitro studies as well as control compounds at optimal concentrations which are determined by the methods described above. At the end of the treatment period, treated and untreated cells are analyzed by one or more methods specific for the assay to determine phenotypic outcomes and endpoints.

[0214] Phenotypic endpoints include changes in cell morphology over time or treatment dose as well as changes in levels of cellular components such as proteins, lipids, nucleic acids, hormones, saccharides or metals. Measurements of cellular status which include pH, stage of the cell cycle, intake or excretion of biological indicators by the cell, are also endpoints of interest.

[0215] Analysis of the genotype of the cell (measurement of the expression of one or more of the genes of the cell) after treatment is also used as an indicator of the efficacy or potency of the HIF1-beta inhibitors. Hallmark genes, or those genes suspected to be associated with a specific disease state, condition, or phenotype, are measured in both treated and untreated cells.

Example 12

RNA Isolation

[0216] Poly(A)+ mRNA Isolation

[0217] Poly(A)+ mRNA was isolated according to Miura et al., (*Clin. Chem.*, 1996, 42, 1758-1764). Other methods for poly(A)+ mRNA isolation are routine in the art. Briefly, for cells grown on 96-well plates, growth medium was removed

from the cells and each well was washed with 200 μ L cold PBS. 60 μ L lysis buffer (10 mM Tris-HCl, pH 7.6, 1 mM EDTA, 0.5 M NaCl, 0.5% NP-40, 20 mM vanadyl-ribonucleoside complex) was added to each well, the plate was gently agitated and then incubated at room temperature for five minutes. 55 μ L of lysate was transferred to Oligo d(T) coated 96-well plates (AGCT Inc., Irvine Calif.). Plates were incubated for 60 minutes at room temperature, washed 3 times with 200 μ L of wash buffer (10 mM Tris-HCl pH 7.6, 1 mM EDTA, 0.3 M NaCl). After the final wash, the plate was blotted on paper towels to remove excess wash buffer and then air-dried for 5 minutes. 60 μ L of elution buffer (5 mM Tris-HCl pH 7.6), preheated to 70° C., was added to each well, the plate was incubated on a 90° C. hot plate for 5 minutes, and the eluate was then transferred to a fresh 96-well plate.

[0218] Cells grown on 100 mm or other standard plates may be treated similarly, using appropriate volumes of all solutions.

Total RNA Isolation

[0219] Total RNA was isolated using an RNEASY 96™ kit and buffers purchased from Qiagen Inc. (Valencia, Calif.) following the manufacturer's recommended procedures. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well was washed with 200 μ L cold PBS. 150 μ L Buffer RLT was added to each well and the plate vigorously agitated for 20 seconds. 150 μ L of 70% ethanol was then added to each well and the contents mixed by pipetting three times up and down. The samples were then transferred to the RNEASY 96™ well plate attached to a QIAVAC™ manifold fitted with a waste collection tray and attached to a vacuum source. Vacuum was applied for 1 minute. 500 μ L of Buffer RW1 was added to each well of the RNEASY 96™ plate and incubated for 15 minutes and the vacuum was again applied for 1 minute. An additional 500 μ L of Buffer RW1 was added to each well of the RNEASY 96™ plate and the vacuum was applied for 2 minutes. 1 mL of Buffer RPE was then added to each well of the RNEASY 96™ plate and the vacuum applied for a period of 90 seconds. The Buffer RPE wash was then repeated and the vacuum was applied for an additional 3 minutes. The plate was then removed from the QIAVAC™ manifold and blotted dry on paper towels. The plate was then re-attached to the QIAVAC™ manifold fitted with a collection tube rack containing 1.2 mL collection tubes. RNA was then eluted by pipetting 140 μ L of RNase free water into each well, incubating 1 minute, and then applying the vacuum for 3 minutes.

[0220] The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia Calif.). Essentially, after lysing of the cells on the culture plate, the plate is transferred to the robot deck where the pipetting, DNase treatment and elution steps are carried out.

Example 13

Real-time Quantitative PCR Analysis of HIF1-beta mRNA Levels

[0221] Quantitation of HIF1-beta mRNA levels was accomplished by real-time quantitative PCR using the ABI PRISM™ 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, Calif.) according to manufacturer's instructions. This is a closed-tube, non-gel-

based, fluorescence detection system which allows high-throughput quantitation of polymerase chain reaction (PCR) products in real-time. As opposed to standard PCR in which amplification products are quantitated after the PCR is completed, products in real-time quantitative PCR are quantitated as they accumulate. This is accomplished by including in the PCR reaction an oligonucleotide probe that anneals specifically between the forward and reverse PCR primers, and contains two fluorescent dyes. A reporter dye (e.g., FAM or JOE, obtained from either PE-Applied Biosystems, Foster City, Calif., Operon Technologies Inc., Alameda, Calif. or Integrated DNA Technologies Inc., Coralville, Iowa) is attached to the 5' end of the probe and a quencher dye (e.g., TAMRA, obtained from either PE-Applied Biosystems, Foster City, Calif., Operon Technologies Inc., Alameda, Calif. or Integrated DNA Technologies Inc., Coralville, Iowa) is attached to the 3' end of the probe. When the probe and dyes are intact, reporter dye emission is quenched by the proximity of the 3' quencher dye. During amplification, annealing of the probe to the target sequence creates a substrate that can be cleaved by the 5'-exonuclease activity of Taq polymerase. During the extension phase of the PCR amplification cycle, cleavage of the probe by Taq polymerase releases the reporter dye from the remainder of the probe (and hence from the quencher moiety) and a sequence-specific fluorescent signal is generated. With each cycle, additional reporter dye molecules are cleaved from their respective probes, and the fluorescence intensity is monitored at regular intervals by laser optics built into the ABI PRISM™ Sequence Detection System. In each assay, a series of parallel reactions containing serial dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after antisense oligonucleotide treatment of test samples.

[0222] Prior to quantitative PCR analysis, primer-probe sets specific to the target gene being measured are evaluated for their ability to be "multiplexed" with a GAPDH amplification reaction. In multiplexing, both the target gene and the internal standard gene GAPDH are amplified concurrently in a single sample. In this analysis, mRNA isolated from untreated cells is serially diluted. Each dilution is amplified in the presence of primer-probe sets specific for GAPDH only, target gene only ("single-plexing"), or both (multiplexing). Following PCR amplification, standard curves of GAPDH and target mRNA signal as a function of dilution are generated from both the single-plexed and multiplexed samples. If both the slope and correlation coefficient of the GAPDH and target signals generated from the multiplexed samples fall within 10% of their corresponding values generated from the single-plexed samples, the primer-probe set specific for that target is deemed multiplexable. Other methods of PCR are also known in the art.

[0223] Gene target quantities are obtained by real-time PCR. Prior to the real-time PCR, isolated RNA is subjected to a reverse transcriptase (RT) reaction, for the purpose of generating complementary DNA (cDNA). Reverse transcriptase and PCR reagents were obtained from Invitrogen Corporation, (Carlsbad, Calif.). RT, real-time PCR reactions were carried out by adding 20 μ L PCR cocktail (2.5 $\times$ PCR buffer minus $MgCl_2$, 6.6 mM $MgCl_2$, 375 μ M each of dATP, dCTP, dGTP and dTTP, 375 nM each of forward primer and reverse primer, 125 nM of probe, 4 Units RNase inhibitor, 1.25 Units PLATINUM® Taq, 5 Units MuLV reverse transcriptase, and 2.5 $\times$ ROX dye) to 96-well plates containing 30 μ L total RNA

solution (20-200 ng). The RT reaction was carried out by incubation for 30 minutes at 48° C. Following a 10 minute incubation at 95° C. to activate the PLATINUM® Taq, 40 cycles of a two-step PCR protocol were carried out: 95° C. for 15 seconds (denaturation) followed by 60° C. for 1.5 minutes (annealing/extension). The method of obtaining gene target quantities by RT, real-time PCR is herein referred to as real-time PCR.

[0224] Gene target quantities obtained by real-time PCR were normalized using either the expression level of GAPDH, a gene whose expression is constant, or by quantifying total RNA using RiboGreen™ (Molecular Probes, Inc. Eugene, Oreg.). GAPDH expression is quantified by real-time PCR by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RiboGreen™ RNA quantification reagent (Molecular Probes, Inc. Eugene, Oreg.). Methods of RNA quantification by RiboGreen™ are taught in Jones, L. J., et al, (Analytical Biochemistry, 1998, 265, 368-374).

[0225] In this assay, 170 µL of RiboGreen™ working reagent (RiboGreen™ reagent diluted 1:350 in 10 mM Tris-HCl, 1 mM EDTA, pH 7.5) was pipetted into a 96-well plate containing 30 µL purified, cellular RNA. The plate was read in a CytoFluor 4000 (PE Applied Biosystems) with excitation at 485 nm and emission at 530 nm.

[0226] Probes and primers to human HIF1-beta were designed to hybridize to a human HIF1-beta sequence, using published sequence information (Genbank accession number BC028362.1, incorporated herein as SEQ ID NO: 4). For human HIF1-beta the PCR primers were:

forward primer: AGCAGAGGGTGTGGGTGTCT (SEQ ID NO: 5)

reverse primer: TGGCGGTTGTTGAACATGTT (SEQ ID NO: 6) and the PCR probe was: FAM-CCAGCAGCCTCAT-CATCGTTCA-TAMRA

(SEQ ID NO: 7) where FAM is the fluorescent dye and TAMRA is the quencher dye. For human GAPDH the PCR primers were:

forward primer: GAAGGTGAAGTCCGAGTC (SEQ ID NO: 8)

reverse primer: GAAGATGGTGATGGGATTTC (SEQ ID NO: 9) and the PCR probe was: 5' JOE-CAAGCTTCCCGT-TCTCAGCC-TAMRA 3' (SEQ ID NO: 10) where JOE is the fluorescent reporter dye and TAMRA is the quencher dye.

[0227] Probes and primers to mouse HIF1-beta were designed to hybridize to a mouse HIF1-beta sequence, using published sequence information (GenBank accession number BC012870.1, incorporated herein as SEQ ID NO: 11). For mouse HIF1-beta the PCR primers were:

forward primer: GGCATCTCCTCCAGCACTGT (SEQ ID NO: 12)

reverse primer: GGTAAGACCACTATTCCTGAAAT-TCTCT (SEQ ID NO: 13) and the PCR

probe was: FAM-TCCCTCCTAACCCCGGCCG-TAMRA (SEQ ID NO: 14) where FAM is the fluorescent reporter dye and TAMRA is the quencher dye.

For mouse GAPDH the PCR primers were:

forward primer: GGCAAATCAACGGCACAGT (SEQ ID NO: 15)

reverse primer: GGGTCTCGCTCCTGGAAGAT (SEQ ID NO: 16) and the PCR probe was: 5' JOE-AAGGC-

CGAGAATGGGAAGCTTGTCATC-TAMRA 3' (SEQ ID NO: 17) where JOE is the fluorescent reporter dye and TAMRA is the quencher dye.

Example 14

Northern Blot Analysis of HIF1-Beta mRNA Levels

[0228] Eighteen hours after antisense treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAzol™ (TEL-TEST "B" Inc., Friendswood, Tex.). Total RNA was prepared following manufacturer's recommended protocols. Twenty micrograms of total RNA was fractionated by electrophoresis through 1.2% agarose gels containing 1.1% formaldehyde using a MOPS buffer system (AM-RESCO, Inc. Solon, Ohio). RNA was transferred from the gel to HYBOND™-N+ nylon membranes (Amersham Pharmacia Biotech, Piscataway, N.J.) by overnight capillary transfer using a Northern/Southern Transfer buffer system (TEL-TEST "B" Inc., Friendswood, Tex.). RNA transfer was confirmed by UV visualization. Membranes were fixed by UV cross-linking using a STRATALINKERT™ UV Crosslinker 2400 (Stratagene, Inc, La Jolla, Calif.) and then probed using QUICKHYB™ hybridization solution (Stratagene, La Jolla, Calif.) using manufacturer's recommendations for stringent conditions.

[0229] To detect human HIF1-beta, a human HIF1-beta specific probe was prepared by PCR using the forward primer AGCAGAGGGTGTGGGTGTCT (SEQ ID NO: 5) and the reverse primer TGGCGGTTGTTGAACATGTT (SEQ ID NO: 6). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, Calif.).

[0230] To detect mouse HIF1-beta, a mouse HIF1-beta specific probe was prepared by PCR using the forward primer GGCATCTCCTCCAGCACTGT (SEQ ID NO: 12) and the reverse primer GGTAAGACCACTATTCCTGAAAT-TCTCT (SEQ ID NO: 13). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for mouse glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, Calif.).

[0231] Hybridized membranes were visualized and quantitated using a PHOSPHORIMAGER™ and IMAGEQUANT™ Software V3.3 (Molecular Dynamics, Sunnyvale, Calif.). Data was normalized to GAPDH levels in untreated controls.

Example 15

Antisense Inhibition of Human HIF1-Beta Expression by Chimeric Phosphorothioate Oligonucleotides Having 2'-MOE Wings and a Deoxy Gap

[0232] In accordance with the present invention, a series of antisense compounds was designed to target different regions of the human HIF1-beta RNA, using published sequences (GenBank accession number BC028362.1, incorporated herein as SEQ ID NO: 4, nucleotides 336578 to 404364 of Genbank accession number NT_021907.12, the complement of which is incorporated herein as SEQ ID NO: 18, GenBank accession number N72808.1, incorporated herein as SEQ ID NO: 19, and GenBank accession number AL834279.1, incorporated herein as SEQ ID NO: 20). The compounds are shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number on the particular target

sequence to which the compound binds. All compounds in Table 1 are chimeric oligonucleotides (“gapmers”) 20 nucleotides in length, composed of a central “gap” region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide “wings”. The wings are composed of 2'- β -methoxyethyl nucleotides, also known as 2'-MOE nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucle-

otide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human HIF1-beta mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments in which T-24 cells were treated with 100 nM of antisense oligonucleotides of the present invention. The positive control for each datapoint is identified in the table by sequence ID number. If present, “N.D.” indicates “no data”.

TABLE 1

Inhibition of human HIF1-beta mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap						
ISIS #	REGION	TARGET		% INHIB	SEQ ID NO	CONTROL SEQ ID NO
		SEQ ID NO	TARGET SEQUENCE SITE (5' to 3')			
311073	Intron 1	18	1578 acacacatatctcaaggccc	65	21	2
311074	Intron 1	18	10523 aagggagcagaggactccct	6	22	2
311075	Intron 1	18	15791 caagatcaggctgggaaca	25	23	2
311076	Intron 2	18	23071 cccctaactctggtcacctgt	71	24	2
311077	Intron 8: Exon 9 junction	18	44694 actgccacacctgtttcaag	51	25	2
311078	Intron 13	18	52827 taggaataataacttatttc	0	26	2
311079	Exon 21: Intron 21 junction	18	63922 actctcttacctggaagacc	4	27	2
311080	5'UTR	4	19 caagatggcggcttcagcag	3	28	2
311081	5'UTR	4	80 ggaaaagaaaggccactccc	0	29	2
311082	Start Codon	4	163 gccgccatggccgcagatgc	87	30	2
311083	Coding	4	199 ggtacatctgatgtcatttc	38	31	2
311084	Coding	4	281 cttaatagccctctggacaa	29	32	2
311085	Coding	4	308 atcatcaaaatccagccctg	42	33	2
311086	Coding	4	388 tccgacctggcaaacgctc	52	34	2
311087	Coding	4	393 catcatccgacctggcaaac	17	35	2
311088	Coding	4	432 attttccctggcaagtctct	55	36	2
311089	Coding	4	472 ctgtcatcttgttcctgcgc	69	37	2
311090	Coding	4	494 tctgacagttctgtgatgta	82	38	2
311091	Coding	4	527 ttctgagccagggcactaca	83	39	2
311092	Coding	4	532 ctgggttttcgagccagggca	76	40	2
311093	Coding	4	652 aatgtttcagttcctgatca	56	41	2
311094	Coding	4	658 agatcaaatgtttcagttcc	66	42	2
311095	Coding	4	663 ctccaagatcaaatgtttca	43	43	2
311096	Coding	4	668 gctgcctccaagatcaaatg	55	44	2
311097	Coding	4	673 catctgctgcctccaagatc	73	45	2
311098	Coding	4	678 aaagccatctgtgcctcca	80	46	2
311099	Coding	4	804 atcatctgggtgcacctgat	76	47	2
311100	Coding	4	810 atccacatcatctgggtgca	80	48	2

TABLE 1-continued

Inhibition of human HIF1-beta mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap						
ISIS #	REGION	TARGET SEQ ID NO	TARGET SEQUENCE SITE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
311101	Coding	4	815 agtttatccacatcatctgg	43	49	2
311102	Coding	4	892 cctttttcactgttccagtc	81	50	2
311103	Coding	4	900 ctgaccttcctttttcactg	68	51	2
311104	Coding	4	906 agactgctgaccttcctttt	63	52	2
311105	Coding	4	1029 tccattcctgcatctgttcc	53	53	2
311106	Coding	4	1036 agccaagtccattcctgcat	84	54	2
311107	Coding	4	1139 gcctctgggtcatcatctgg	79	55	2
311108	Coding	4	1200 gggagaactagttacctgca	48	56	2
311109	Coding	4	1205 cagttgggagaactagttac	43	57	2
311110	Coding	4	1210 ctgtacagttgggagaacta	74	58	2
311111	Coding	4	1215 catgtctgtacagttgggag	34	59	2
311112	Coding	4	1220 ttactcatgtctgtacagtt	84	60	2
311113	Coding	4	1251 tcgggagatgaactctgttg	65	61	2
311114	Coding	4	1256 ttgtgtcgggagatgaactc	49	62	2
311115	Coding	4	1261 caatgttgtgtcgggagatg	57	63	2
311116	Coding	4	1310 tagccaacagtagccacaca	48	64	2
311117	Coding	4	1315 gctggtagccaacagtagcc	51	65	2
311118	Coding	4	1320 ctgtggttggtagccaacag	52	66	2
311119	Coding	4	1343 acaatattctttcctaagag	27	67	2
311120	Coding	4	1405 atttcactacctgttgaag	67	68	2
311121	Coding	4	1418 acttgcccttttaatttcac	55	69	2
311122	Coding	4	1423 acagcacttggccttttaat	63	70	2
311123	Coding	4	1434 gaacatgacagacagcactt	62	71	2
311124	Coding	4	1551 gttcttcacattggtgttgg	68	72	2
311125	Coding	4	1556 ctagagttcttcacattggt	56	73	2
311126	Coding	4	1706 ccattctcttcctggtaccat	77	74	2
311127	Coding	4	1862 ttactctgatccgcattgat	49	75	2
311128	Coding	4	1871 gagatgcctttactctgac	67	76	2
311129	Coding	4	1876 tggaggagatgcctttactc	84	77	2
311130	Coding	4	1881 agtgctggaggagatgcctt	75	78	2
311131	Coding	4	1953 gaaattctctgccggccggg	70	79	2
311132	Coding	4	1958 ttcttgaaattctctgccgg	67	80	2
311133	Coding	4	1967 agaccactattcctgaaatt	15	81	2
311134	Coding	4	1990 ggacaatggttacaggaggg	68	82	2

TABLE 1-continued

Inhibition of human HIF1-beta mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap						
ISIS #	REGION	TARGET SEQ ID NO	TARGET SEQUENCE SITE (5' to 3')	% INHIB	SEQ ID CONTROL NO	SEQ ID NO
311135	Coding	4	1995 tggctggacaatggttacag	80	83	2
311136	Coding	4	2276 gtctcaggagcaaagttaga	48	84	2
311137	Coding	4	2339 cactgtggccagacacccac	65	85	2
311138	Coding	4	2349 ctggccctgccactgtggcc	42	86	2
311139	Coding	4	2354 ggctgctggccctgccactg	85	87	2
311140	Coding	4	2507 ggaaacatagttagatcagg	66	88	2
311141	Stop Codon	4	2531 caatagttctattctgaaaa	21	89	2
311142	Stop Codon	4	2537 tcacccaatagttctatttc	27	90	2
311143	Stop Codon	4	2542 tatcctcacccaatagtttc	24	91	2
311144	3'UTR	4	2616 agaggaaacttttattctgtt	51	92	2
311145	3'UTR	4	2621 aaggagaggaacttttatt	0	93	2
311146	3'UTR	4	2873 atccaaggcaaacagtggat	66	94	2
311147	3'UTR	4	3791 gtccaggcccatctatcat	57	95	2
311148	3'UTR	4	4429 tgaaaatctttgctacatgt	72	96	2
311149	5'UTR	19	231 ccaggtggtcacatctggtc	33	97	2
311150	Exon1: Exon1A junction	20	162 tgagtccaagatcaggcggg	18	98	2

[0233] As shown in Table 1, the majority of antisense compounds targeting human HIF1-beta resulted in inhibition of HIF1-beta mRNA levels. Treatment of cells with antisense compounds represented by SEQ ID NOs: 21, 23-25, 30-34, 36-80, 82-92 and 94-97 resulted in at least 20% inhibition of HIF1-beta mRNA; SEQ ID NOs: 21, 24, 25, 30, 33, 34, 36-58, 60-66, 68-80, 82-88, 92 and 94-96 resulted in at least 40% inhibition of HIF1-beta mRNA; SEQ ID NOs: 21, 24, 25, 30, 34, 36-42, 44-48, 50-55, 58, 60, 61, 63, 65, 66, 68-74, 76-80, 82, 83, 85, 87, 88, 92 and 94-96 resulted in at least 50% inhibition of HIF1-beta mRNA; SEQ ID NOs: 21, 24, 30, 37-40, 42, 45-48, 50-52, 54, 55, 58, 60, 61, 68, 70-72, 74, 76-80, 82, 83, 85, 87, 88, 94 and 96 resulted in at least 60% inhibition of HIF1-beta mRNA; SEQ ID NOs: 24, 30, 38-40, 45-48, 50, 54, 55, 58, 60, 74, 77-79, 83, 87 and 96 resulted in at least 70% inhibition of HIF1-beta mRNA; and SEQ ID NOs: 30, 38, 39, 46, 48, 50, 54, 60, 77, 83 and 87 resulted in at least 80% inhibition of HIF1-beta mRNA.

Example 16

Antisense Inhibition of Mouse HIF1-Beta Expression by Chimeric Phosphorothioate Oligonucleotides Having 2'-MOE Wings and a Deoxy Gap

[0234] In accordance with the present invention, a second series of antisense compounds was designed to target differ-

ent regions of the mouse HIF1-beta RNA, using published sequences (GenBank accession number BC012870.1, incorporated herein as SEQ ID NO: 11, nucleotides 1145000 to 1210000 of GenBank accession number NW_000199.1, incorporated herein as SEQ ID NO: 99, GenBank accession number AK040475.1, incorporated herein as SEQ ID NO: 100, GenBank accession number AK028546.1, incorporated herein as SEQ ID NO: 101, GenBank accession number BG083773.1, incorporated herein as SEQ ID NO: 102, and GenBank accession number AK049738.1, incorporated herein as SEQ ID NO: 103). The compounds are shown in Table 2. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the compound binds. All compounds in Table 2 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-O-methoxyethyl nucleotides, also known as 2'-MOE nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on mouse HIF1-beta mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments in which b.END cells were treated with 40 nM of antisense oligonucleotides of the present invention. The positive control for each datapoint is identified in the table by sequence ID number. If present, "N.D." indicates "no data".

TABLE 2

Inhibition of mouse HIF1-beta mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap						
ISIS # REGION	TARGET SEQ ID NO	TARGET SEQUENCE SITE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO	
347985 Intron 1	99	12686 gattccagcagaaacaagat	76	104	2	
347986 Intron 2	99	20208 agtaccataaccaggaagag	82	105	2	
347987 Intron 3: Exon 4 junction	99	28425 atcatcgcatctgaaaagaa	51	106	2	
347988 Exon 11: Intron 11 junction	99	51989 tcatacttgccctgcagcctg	59	107	2	
347989 5'UTR	11	3 agattaggcaccttaccgcc	80	108	2	
347990 Start Codon	11	98 gccgccatggctgagatggc	73	109	2	
347991 Start Codon	11	111 gttagctgtagtcgcccga	88	110	2	
347992 Coding	11	121 tcattttctgggttagctgta	75	111	2	
347993 Coding	11	131 acatctgatgtcatttctgg	79	112	2	
347994 Coding	11	163 ttccagaagcaatggaggga	69	113	2	
347995 Coding	11	195 agtcctccaccttgaatcc	41	114	2	
347996 Coding	11	221 cgtcgcttaatagccctctg	81	115	2	
347997 Coding	11	231 cagccctgaccgtcgcttaa	83	116	2	
347998 Coding	11	241 catcaaaatccagccctgac	29	117	2	
347999 Coding	11	317 ctggcaaaccgctctttgtc	47	118	2	
348000 Coding	11	327 atcatccgacctggcaaacc	85	119	2	
348001 Coding	11	337 agctctgctcatcatccgac	41	120	2	
348002 Coding	11	355 gtctctctttatccgcagag	89	121	2	
348003 Coding	11	362 ctggcaagtctctctttatc	66	122	2	
348004 Coding	11	367 tttccctggcaagtctctct	56	123	2	
348005 Coding	11	372 atgattttccctggcaagtc	75	124	2	
348006 Coding	11	414 gtaagctgtcatcttgttcc	73	125	2	
348007 Coding	11	424 gttctgtgatgtaagctgtc	49	126	2	
348008 Coding	11	477 tagcttgtctggttttcgag	63	127	2	
348009 Coding	11	591 caaatgtttcagttcctgat	82	128	2	
348010 Coding	11	622 taaacagaaagccatctgct	83	129	2	
348011 Coding	11	686 tggttcaaacgggagtcac	39	130	2	
348012 Coding	11	763 gctgctctcgaagtttatcc	58	131	2	
348013 Coding	11	858 gcacatcctcatggaagact	90	132	2	
348014 Coding	11	929 ttcattggaacagggtccac	84	133	2	
348015 Coding	11	939 gctcagtctattcatggaaa	76	134	2	
348016 Coding	11	949 tcctcaaaaagctcagtcta	56	135	2	
348017 Coding	11	959 ctgcatctgttctcaaaaa	86	136	2	

TABLE 2-continued

Inhibition of mouse HIF1-beta mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap						
ISIS # REGION	TARGET SEQ ID NO	TARGET SEQUENCE SITE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO	
348018 Coding	11	1015 tgcagtggactaccacaaag	68	137	2	
348019 Coding	11	1081 ggccagcctctgggtcatca	89	138	2	
348020 Coding	11	1097 cagaatttgctccccctggcc	73	139	2	
348021 Coding	11	1107 ggccactaggcagaatttgc	79	140	2	
348022 Coding	11	1119 cagcctgccaatggccacta	70	141	2	
348023 Coding	11	1211 gtgaatatcccttcaatgtt	74	142	2	
348024 Coding	11	1241 acagtagccacacacgatg	79	143	2	
348025 Coding	11	1291 gacaaaattctacaatattc	53	144	2	
348026 Coding	11	1302 gtcttcaggatgacaaaatt	79	145	2	
348027 Coding	11	1312 gaagttgttggtcttcagga	65	146	2	
348028 Coding	11	1323 gctgtctcttagaagttgtt	25	147	2	
348029 Coding	11	1333 cctgctgaaagctgtctctt	76	148	2	
348030 Coding	11	1343 aatttcaccacctgctgaaa	56	149	2	
348031 Coding	11	1408 tcattccacagccattctcgg	75	150	2	
348032 Coding	11	1504 gtggttcctggctagagttc	58	151	2	
348033 Coding	11	1550 gtcggacctagctgtgacct	80	152	2	
348034 Coding	11	1579 ctgtacccatctctagggat	79	153	2	
348035 Coding	11	1651 ccagcccatctcttctctggt	23	154	2	
348036 Coding	11	1681 ggacagaaacctgggaatga	76	155	2	
348037 Coding	11	1719 gggcttgctgtgttctgac	70	156	2	
348038 Coding	11	1742 aagagaccttctgacttctc	57	157	2	
348039 Coding	11	1855 cctgggagaaacagctgttgg	84	158	2	
348040 Coding	11	1865 aatgagctgccctgggagaa	83	159	2	
348041 Coding	11	1875 gttaggaggaatgagctgc	69	160	2	
348042 Coding	11	1906 cactattctgaaattctct	65	161	2	
348043 Coding	11	1958 atctgccctgcagaagatga	58	162	2	
348044 Coding	11	2083 aagaacgagctcttggtgta	70	163	2	
348045 Coding	11	2110 tctgaaagtgttcacacca	51	164	2	
348046 Coding	11	2219 gtctcaggaggaaagtggga	88	165	2	
348047 Coding	11	2287 cctgccactgtggccagaca	77	166	2	
348048 Coding	11	2379 ttcttgaaagacctcaggct	52	167	2	
348049 Coding	11	2399 tctcccagcatggacagcat	68	168	2	
348050 Stop Codon	11	2475 ccaatagttctattcggaaa	87	169	2	
348051 3'UTR	11	2538 tctgtttacaaaagatttgc	78	170	2	

TABLE 2-continued

Inhibition of mouse HIF1-beta mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap						
ISIS #	REGION	TARGET	TARGET SEQUENCE	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
		SEQ ID NO	SITE (5' to 3')			
348052	5'UTR	100	10 cggatccaagatggcggac	88	171	2
348053	3'UTR	100	2358 ctccaacaagcctgagacc	87	172	2
348054	Coding	101	352 atgattttccctggcaaacc	79	173	2
348055	Coding	101	2031 ggcacctgggcggcaaagcc	60	174	2
348056	Coding	102	608 agacttttccccacatattc	67	175	2
348057	5'UTR	103	50 taacctatgtattcagtgat	34	176	2
311090	Coding	11	431 tctgacagttctgtgatgta	75	38	2
311091	Coding	11	464 ttctgagccagggcactaca	82	39	2
311112	Coding	11	1157 ttactcatgtctgtacagtt	82	60	2
311129	Coding	11	2819 tggaggagatgcctttactc	75	77	2
311130	Coding	11	1824 agtgctggaggagatgcctt	78	78	2

[0235] As shown in Table 1, the majority of antisense compounds targeting mouse HIF1-beta resulted in inhibition of HIF1-beta mRNA levels. Treatment of cells with antisense compounds represented by SEQ ID NOs: 38, 39, 60, 77, 78, 104-153 and 155-176 resulted in at least 25% inhibition of HIF1-beta mRNA; SEQ ID NOs: 38, 39, 60, 77, 78, 104-113, 115, 116, 119, 121-125, 127-129, 131-146, 148-153 and 155-175 resulted in at least 50% inhibition of HIF1-beta mRNA; 38, 39, 60, 77, 78, 104, 105, 108-113, 115, 116, 119, 121, 122, 124, 125, 127-129, 132-134, 136-143, 145, 146, 148, 150, 152, 153, 155, 156, 158-161, 163, 165, 166 and 168 resulted in at least 60% inhibition of HIF1-beta mRNA; SEQ ID NOs: 38, 39, 60, 77, 78, 104, 105, 108-112, 115, 116, 119, 121, 124, 125, 128, 129, 132-134, 136, 138-143, 145, 148, 150, 152, 153, 155, 156, 158, 159, 163, 165, 166 and 169-173 resulted in at least 70% inhibition of HIF1-beta mRNA; and SEQ ID NOs: 39, 60, 105, 108, 110, 115, 116, 119, 121, 128, 129, 132, 133, 136, 138, 152, 158, 159, 165, 169, 171 and 172 resulted in at least 80% inhibition of HIF1-beta mRNA.

Example 17

Targeting of Individual Oligonucleotides to Specific Variants of Human HIF1-Beta

[0236] A search of the National Center for Biotechnology Information database revealed alternative mRNA variants of human HIF1-beta which are the result of alternative splicing. The sequence identified as Genbank accession number N72808.1 represents a variant of HIF1-beta designated herein as HIF1-beta-1 (incorporated herein as SEQ ID NO: 19). The sequence identified as Genbank accession number AL834279.1 represents a variant of HIF1-beta designated herein as HIF1-beta-2 (incorporated herein as SEQ ID NO: 20).

[0237] It is advantageous to selectively inhibit the expression of one or more variants of HIF1-beta. Consequently, in one embodiment of the present invention are oligonucleotides that selectively target, hybridize to, and specifically inhibit one or more, but fewer than all the variants of HIF1-beta. The oligonucleotides of the present invention that selectively target human HIF1-beta variants are presented in Table 4.

TABLE 4

Targeting of individual oligonucleotides to specific variants of human HIF1-beta				
ISIS #	SEQ ID NO	Target Site	Target Variant	Target SEQ ID NO
311149	97	231	HIF1-beta-1	19
331150	98	162	HIF1-beta-2	20

Example 18

Targeting of Individual Oligonucleotides to Specific Variants of Mouse HIF1-Beta

[0238] A search of the National Center for Biotechnology Information database revealed alternative mRNA variants of mouse HIF1-beta which are the result of alternative splicing. The sequence identified as Genbank accession number AK040475.1 represents a variant of HIF1-beta designated herein as HIF1-beta-3 (incorporated herein as SEQ ID NO: 100). The sequence identified as Genbank accession number AK028546.1 represents a variant of HIF1-beta designated herein as HIF1-beta-4 (incorporated herein as SEQ ID NO: 101). The sequence identified as Genbank accession number BG083773.1 represents a variant of HIF1-beta designated herein as HIF1-beta-5 (incorporated herein as SEQ ID NO: 102). The sequence identified as Genbank accession number

AK049738.1 represents a variant of HIF1-beta designated herein as HIF1-beta-6 (incorporated herein as SEQ ID NO: 103).

[0239] It is advantageous to selectively inhibit the expression of one or more variants of HIF1-beta. Consequently, in one embodiment of the present invention are oligonucleotides that selectively target, hybridize to, and specifically inhibit one or more, but fewer than all the variants of mouse HIF1-beta. The oligonucleotides of the present invention that selectively target mouse HIF1-beta variants are presented in Table 5.

TABLE 5

Targeting of individual oligonucleotides to specific variants of mouse HIF1-beta				
ISIS #	SEQ ID NO	Target Site	Target Variant	Target SEQ ID NO
348052	171	10	HIF1-beta-3	100
348053	172	2358	HIF1-beta-3	100
348053	172	1543	HIF1-beta-6	103
348054	173	352	HIF1-beta-4	101
348054	173	149	HIF1-beta-5	102
348055	174	2031	HIF1-beta-4	101
348056	175	608	HIF1-beta-5	102
348057	176	50	HIF1-beta-6	103

Example 19

Expression of HIF1-Beta in Various Human Cell Lines

[0240] U87-MG human glioblastoma, PC-3 human prostate cancer, JEG-3 human choriocarcinoma, HeLa human cervical cancer, SK-N-BE(2) neuroblastoma, MCF-7 human breast cancer, 786-O human clear-cell renal cell carcinoma, Calu-1 human lung cancer, and Hep3B human hepatocellular carcinoma cells were purchased from American Type Culture Collection (ATCC; Manassas, Va.) and cultured according to ATCC directions. Human umbilical endothelial cells (HUVEC) were obtained from Cascade Biologics (Portland, Oreg.). Hypoxic treatments of cells (0.5-0.8×10⁶/60 mm dish or 1-2×10⁶/100 mm dish) were performed at 1% O₂ in a chamber controlled by ProOx oxygen sensor (BioSpherix, Redfield, N.Y.) for 18 h. To achieve the optimal hypoxic induction, 2 or 5 ml of medium was used for 60 mm and 100 mm culture dishes, respectively, during incubation. CoCl₂ (150 μM) was added to the cells to mimic hypoxic condition in some experiments.

[0241] After 18 h of culture at normoxia, hypoxia, or with CoCl₂, cells were harvested and whole cell lysates prepared with RIPA buffer containing protease inhibitor cocktails (Roche), 0.5 mM sodium orthovanadate, 10 mM β-glycerophosphate, 250 ng/ml ubiquitin aldehyde (Sigma-Aldrich), and 400 nM epoxomicin (Alexis). Lysates were separated on 10% SDS-PAGE and transferred to PVDF membranes (Amersham Biosciences). Immunoblotting was performed with the following antibodies and dilutions: anti-HIF1-beta (BD Transduction Laboratories) at 1:1000; anti-VHL (BD Transduction Laboratories) at 1:500; anti-GLUT-1 (Alpha Diagnostic International) at 1:600, and anti-α-tubulin (Sigma) at 1:2000. Antibodies were diluted in 0.05% Tween-20/Tris-buffered saline (T-TBS) blocking buffer containing 5% non-fat skim milk and incubated with the PVDF membranes at 4° C. overnight, followed by washing with T-TBS for 30 min.

Goat anti-mouse or rabbit IgGs coupled with HRP (BioRad) were used as secondary antibodies at 1:3000. Immunospecific bands were detected by enhanced chemiluminescence plus (ECL-Plus) detection kit (Amersham Biosciences).

[0242] Expression of HIF1-beta was detected under both normoxic and hypoxic conditions; however, levels of expression of HIF1-beta varied among cell lines. HIF1-beta expression was induced under hypoxic conditions and in the presence of CoCl₂ (which mimics hypoxia) in U87-MG human glioblastoma cells and MCF-7 human breast cancer cells. However, expression of HIF1-beta in JEG-3, PC-3, Hep3B, HeLa, 786-O, SK-N-BE(2), Calu-1 and HUVECs was not significantly altered by culturing under hypoxic conditions or in the presence of CoCl₂.

Example 20

Antisense Modulation of HIF1-Beta mRNA Expression in Cancer Cells (Dose Response)

[0243] Hep3B or U87-MG cells were plated in 96-well plates (8-10,000/well) 16 h prior to transfection. Control oligonucleotide ISIS 129688 (SEQ ID NO: 177) or HIF1-beta antisense oligonucleotides ISIS 311082 (SEQ ID NO: 30) and ISIS 311129 (SEQ ID NO: 77) at a concentration of 0, 6.25 or 25 nM were delivered into cells by lipofectin (3 μg/ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen). Both control and HIF1-beta antisense oligonucleotides are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-O-methoxyethyl nucleotides, also known as 2'-MOE nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines.

[0244] The transfection medium (120 μl/well) was switched to low-serum medium (0.1% FBS) 4 h after transfection. Sixty microliters of medium was removed from the well 3 h after media switch and the cells were further incubated at normoxia or hypoxia for 16-20 h.

[0245] Total RNAs were isolated using RNeasy 96 BioRobot 9604 kit (Qiagen) according to the manufacturer's instructions. Quantitative real-time RT-PCR for detection of HIF1-beta mRNA was performed as described in other Examples herein by ABI Prism 7700 Sequence Detector (Applied Biosystems) in 25 or 50 μl reaction volumes. The level of mRNA for each gene was normalized to the amount of total RNA determined by Ribogreen™ (Molecular Probes).

TABLE 6

HIF1-beta mRNA expression in hypoxic Hep3B cells treated with antisense oligonucleotide to HIF1-beta (shown as percent of untreated control cells at normoxia)			
Oligonucleotide	Percent expression of HIF1-beta mRNA after treatment with oligonucleotide at the concentrations shown:		
	0 nM	6.25 nM	25 nM
129688	78	78	77
311082	79	50	20
311129	77	70	30

TABLE 7

HIF1-beta mRNA expression in hypoxic U87-MG cells treated with antisense oligonucleotide to HIF1-beta (shown as percent of untreated control cells at normoxia)			
Oligonucleotide	Percent expression of HIF1-beta mRNA after treatment with oligonucleotide at the concentrations shown:		
	0 nM	6.25 nM	25 nM
129688	78	78	77
311082	79	50	20
311129	77	70	20

[0246] HIF1-beta antisense oligonucleotides ISIS 311082 and ISIS 311129 specifically inhibited mRNA expression of HIF1-beta in both Hep3B and U87-MG cells in a dose-dependent manner.

Example 21

Antisense Modulation of HIF1-Beta Protein Expression

[0247] U87-MG cells were plated in 10 cm dishes (1-2x10⁶ cells/dish) 16 h prior to transfection. 100 nM control oligonucleotide (ISIS 129688, SEQ ID NO: 177) or HIF1-beta antisense oligonucleotide (ISIS 311082, SEQ ID NO: 30) were delivered into cells by lipofectin (3 µg/ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen).

[0248] The transfection medium (10 ml/dish) was switched to low-serum medium (0.1% FBS) 4 h after transfection. Five ml of medium was removed from the well 3 h after media switch and the cells were further incubated at normoxia or hypoxia for 16-20 h.

[0249] Following incubation at normoxia or hypoxia, transfected cells were harvested and whole cell lysates prepared with RIPA buffer containing protease inhibitor cocktails (Roche), 0.5 mM sodium orthovanadate, 10 mM β-glycerophosphate, 250 ng/ml ubiquitin aldehyde (Sigma-Aldrich), and 400 nM epoxomicin (Alexis). Lysates were separated on 10% SDS-PAGE and transferred to PVDF membranes (Amersham Biosciences). Immunoblotting was performed with the following antibodies and dilutions: anti-HIF1-BETA (BD Transduction Laboratories) at 1:1000; anti-GLUT-1 (Alpha Diagnostic International) at 1:600, and anti-α-tubulin (Sigma) at 1:2000. Antibodies were diluted in 0.05% Tween-20/Tris-buffered saline (T-TBS) blocking buffer containing 5% nonfat skim milk and incubated with the PVDF membranes at 4° C. overnight, followed by washing with T-TBS for 30 min. Goat anti-mouse or rabbit IgGs coupled with HRP (BioRad) were used as secondary antibodies at 1:3000. Immunospecific bands were detected by enhanced chemiluminescence plus (ECL-Plus) detection kit (Amersham Biosciences).

[0250] The results demonstrated that transfection with HIF1-beta antisense oligonucleotide inhibited HIF1-beta protein expression. Furthermore, protein expression of GLUT-1, a HIF1-beta-responsive gene, was induced under hypoxia in the absence of HIF1-beta antisense oligonucle-

otide, but was nearly eliminated in hypoxic cells transfected with HIF1-beta antisense oligonucleotide.

Example 22

Expression HIF1-Beta-Regulated Genes in Cells Cultured Under Hypoxic Conditions

[0251] Genes whose products are significantly induced by hypoxia (or CoCl₂, a mimic of hypoxia) include erythropoietin (Epo), glucose transporter-1 (GLUT-1), vascular endothelial growth factor (VEGF), phosphoglycerate kinase-1 (PGK-1) and plasminogen activator inhibitor-1 (PAI-1). These genes are regulated by HIF1-beta and are induced under hypoxic conditions to varying extents in different cell lines. To determine mRNA expression levels of Epo, GLUT-1, VEGF, PGK-1 and PAI-1 at normoxia (21% O₂), hypoxia (1% O₂) and in the presence of 150 µM CoCl₂, in HeLa, Hep3B, U87-MG, PC-3 and 786-O cells, RT-PCR was performed. Total RNA was isolated after 18 h of culture using the RNeasy 96 BioRobot 9604 (Qiagen) according to the manufacturer's protocol. Quantitative real-time RT-PCR was performed as described in other Examples herein by ABI Prism 7700 Sequence Detector (Applied Biosystems) in 25 or 50 µl reaction volumes. The level of mRNA for each gene was normalized to the amount of total RNA determined by Ribogreen™ (Molecular Probes).

TABLE 8

VEGF, GLUT-1, PGK-1, PAI-1 and Epo mRNA expression levels at normoxia, hypoxia and 150 µM CoCl ₂ (shown as fold-induction relative to HeLa cells at normoxia)				
Gene	Cell Type	Normoxia	Hypoxia	CoCl ₂
VEGF	HeLa	1	3	2
	Hep3B	4	24	11
	U87-MG	17	46	28
	PC-3	1	2	2
	786-O	6	6	10
GLUT-1	HeLa	1	2.1	1.5
	Hep3B	0.2	1	1
	U87-MG	2.5	3.1	5.3
	PC-3	1	4.1	3.7
	786-O	2.9	3.4	5.7
PGK-1	HeLa	1	3	2
	Hep3B	4	24	10
	U87-MG	16	46	28
	PC-3	1	2	2
	786-O	6	6	9
PAI-1	HeLa	1	1.5	1
	Hep3B	1.5	28	2
	U87-MG	9	24	32
	PC-3	3	4	3
	786-O	2	3	16
Epo	HeLa	1	1	1
	Hep3B	7	260	15
	U87-MG	1	1	1
	PC-3	1	1	1
	786-O	1	1	1

[0252] Although expression levels of the five genes under each condition varied widely among cell lines, VEGF, GLUT-1, PGK-1, PAI-1 and Epo exhibited a trend of increased expression when cells were cultured under hypoxia or in the presence of 150 µM CoCl₂. As previously reported, hypoxia-induced Epo expression occurred only in Hep3B cells.

Example 23

Antisense Inhibition of HIF1-Beta Target Genes

[0253] Hep3B or U87-MG cells were plated in 96-well plates (8-10,000/well) 16 h prior to transfection. Control oli-

gonucleotide ISIS 129688 (SEQ ID NO: 177) or HIF1-beta antisense oligonucleotides ISIS 311082 (SEQ ID NO: 30) and ISIS 311129 (SEQ ID NO: 77) at a concentration of 0, 6.25 or 25 nM were delivered into cells by lipofectin (3 µg/ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen).

[0254] The transfection medium (120 µl/well) was switched to low-serum medium (0.1% FBS) 4 h after transfection. Sixty microliters of medium was removed from the well 3 h after media switch and the cells were further incubated at normoxia or hypoxia for 16-20 h.

[0255] Total RNAs were isolated using RNeasy 96 BioRobot 9604 kit (Qiagen) according to the manufacturer's instructions. Quantitative real-time RT-PCR for detection of GLUT-1, VEGF or Epo mRNA was performed as described in other Examples herein by ABI Prism 7700 Sequence Detector (Applied Biosystems) in 25 or 50 µl reaction volumes. The level of mRNA for each gene was normalized to the amount of total RNA determined by Ribogreen™ (Molecular Probes).

TABLE 9

GLUT-1 mRNA expression in hypoxic Hep3B cells treated with antisense oligonucleotide to HIF1-beta (shown as percent of untreated control cells)				
Oligonucleotide	Percent expression of GLUT-1 mRNA after treatment with oligonucleotide at the concentrations shown:			
	0 nM	6.25 nM	25 nM	
129688	100	85	83	
311082	100	72	34	
311129	100	74	79	

TABLE 10

GLUT-1 mRNA expression in hypoxic U87-MG cells treated with antisense oligonucleotide to HIF1-beta (shown as percent of untreated control cells)				
Oligonucleotide	Percent expression of GLUT-1 mRNA after treatment with oligonucleotide at the concentrations shown:			
	0 nM	6.25 nM	25 nM	
129688	100	100	102	
311082	100	76	28	
311129	100	83	40	

TABLE 11

VEGF mRNA expression in hypoxic U87-MG cells treated with antisense oligonucleotide to HIF1-beta (shown as percent of untreated control cells)				
Oligonucleotide	Percent expression of VEGF mRNA after treatment with oligonucleotide at the concentrations shown:			
	0 nM	6.25 nM	25 nM	
129688	100	101	82	
311082	100	62	26	
311129	100	71	28	

TABLE 12

Epo mRNA expression in hypoxic Hep3B cells treated with antisense oligonucleotide to HIF1-beta (shown as percent of untreated control cells)				
Oligonucleotide	Percent expression of Epo mRNA after treatment with oligonucleotide at the concentrations shown:			
	0 nM	6.25 nM	25 nM	
129688	100	107	114	
311082	100	95	38	
311129	100	100	74	

[0256] As shown in other Examples herein, GLUT-1, Epo and VEGF mRNA expression was induced under hypoxic conditions. HIF1-beta antisense oligonucleotides ISIS 311082 and ISIS 311129 specifically inhibited mRNA expression of GLUT-1, Epo and VEGF in both Hep3B cells (GLUT-1 and Epo) and U87-MG cells (GLUT-1 and VEGF).

Example 24

Antisense Inhibition of Protein Expression of HIF1-Beta Downstream Targets

[0257] U87-MG, HeLa or Hep3B cells were plated in 10 cm dishes (1-2×10⁶ cells/dish) 16 h prior to transfection. 100 nM control oligonucleotide (ISIS 129688, SEQ ID NO: 177) or HIF1-beta antisense oligonucleotide (ISIS 311082, SEQ ID NO: 30) were delivered into cells by lipofectin (3 µg/ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen).

[0258] The transfection medium (10 ml/well) was switched to low-serum medium (0.1% FBS) 4 h after transfection. Five ml of medium was removed from the well 3 h after media switch and the cells were further incubated at normoxia or hypoxia.

[0259] After incubation at normoxia or hypoxia for 16 h, the media was removed and stored at -80° C. prior to use. Levels of VEGF protein in either U87-MG or HeLa cells was determined by Quantikine ELISA kit (R&D Systems) according to the manufacturer's protocol. To determine levels of Epo protein in Hep3B cells, cell culture media was concentrated up to 10% of the original volume by Amicon Ultra (Millipore) and Epo protein was quantitated by Quantikine IVD human Epo ELISA kit (R&D Systems). The obtained

values were normalized to the number of cells (VEGF) or the amount of total protein (Epo) used for the assay.

[0260] Under hypoxic conditions, VEGF protein production in U87-MG cells treated with HIF1-beta antisense oligonucleotide was significantly reduced (approximately 4-fold) relative to cells treated with control oligonucleotide. In HeLa cells, VEGF protein levels were slightly reduced by treatment with HIF1-beta antisense oligonucleotide. In Hep3B cells treated with HIF1-beta antisense oligonucleotide, Epo protein levels were significantly reduced (approximately 15-fold) relative to cells treated with control oligonucleotide. Thus, treatment with HIF1-beta antisense oligonucleotides not only inhibits expression of HIF1-beta, but also results in downregulation of HIF1-beta target genes.

Example 25

Hypoxia-Induced Binding of HIF1-Beta to Hypoxia Response Element (HRE) In Vivo

[0261] To demonstrate binding of HIF1-beta to the hypoxia response element (HRE) on the promoter region of the VEGF gene under hypoxic conditions, chromatin immunoprecipitation (ChIP) assays were performed. U87-MG cells were plated in 10 cm dishes in complete growth media containing 10% FBS at a density of 1×10^6 cells/dish. After 24 h, the media was replaced with low serum media (0.1% FBS) and the cells were incubated at either normoxia or hypoxia for 16 h. After incubation, cells were cross-linked with a 1% formaldehyde solution for 10 min at 37° C. After two washes with cold PBS, cells were processed following the ChIP assay kit protocol (Upstate). For immunoprecipitation, protein extracts were incubated with antibodies to HIF1-beta (10 µg) and mouse IgG (10 µg) at 4° C. for 40 h, followed by 2 h incubation with salmon sperm DNA/Protein A agarose slurry. After extensive washing, the immune/DNA complex was eluted in 500 µl of buffer (1% SDS, 0.1 M NaHCO₃), reverse-crosslinked at 65° C. for 4 h in the presence of 0.2 M NaCl and subjected to proteinase K (Ambion) digestion at 45° C. for 1 h. Samples were extracted with phenol-chloroform-isoamylalcohol, ethanol-precipitated overnight at -80° C. and the DNA was resuspended in water.

[0262] Samples were analyzed by PCR using Accuprime II (Invitrogen) Taq polymerase in the presence of [³²P-dCTP]. PCR products were separated on 6% Tris-borate-EDTA (TBE)-PAGE, dried and exposed to X-ray film at -80° C. The forward (F) and reverse (R) primers used for PCR are as follows:

VEGF I (F): CCTGGCAACATCTGGGGTTGG (SEQ ID NO: 178)

VEGF I (R): CAACAGGCTGGAGTGACTGGGCTCC (SEQ ID NO: 179)

VEGF II (F): GTGGAGACAGGACTAGTGCACGAATG (SEQ ID NO: 180)

VEGF II (R): CTGTGGAGGCATGGACTGAGAATGG (SEQ ID NO: 181)

Epo (F): CTGGGAACCTCCAAATCCCCTGGC (SEQ ID NO: 182)

Epo (R): CTGGGCAGGGTTGGCAGCTGCCTTAC (SEQ ID NO: 183)

[0263] VEGF I primers amplify a region that includes the HRE. VEGF II primers amplify a promoter region upstream of the HRE, therefore this region serves as a negative control. The Epo gene also is a negative control since it is not expressed in U87-MG cells.

[0264] HIF1-beta was not detected on the VEGF HRE at normoxia. However, hypoxia induced the recruitment of HIF1-beta to the VEGF HRE (VEGF I). No binding of HIF1-beta was detected to the regions amplified by the VEGF II or Epo primers.

Example 26

Inhibition of HIF1-Beta Expression In Vivo

[0265] C57B1/6 mice are maintained on a standard rodent diet and are used as control animals. Seven-week old male C57B1/6 mice are injected subcutaneously with oligonucleotides at a dose of 25 mg/kg two times per week for 4 weeks. Saline-injected animals serve as a control. After the treatment period, mice are sacrificed and target levels are evaluated in liver, spleen, adipose and other tissues using RNA isolation and target mRNA expression level quantitation (RT-PCR) as described in other examples herein.

Example 27

Tube Formation Assay to Determine Effect of HIF1-Beta Antisense Inhibitors on Angiogenesis

[0266] Angiogenesis is stimulated by numerous factors that promote interaction of endothelial cells with each other and with extracellular matrix molecules, resulting in the formation of capillary tubes. This process can be reproduced in tissue culture by the formation of tube-like structures by endothelial cells. Loss of tube formation in vitro has been correlated with the inhibition of angiogenesis in vivo (Carmeliet et al., (2000) Nature 407:249-257; and Zhang et al., (2002) Cancer Research 62:2034-42), which supports the use of in vitro tube formation as an endpoint for angiogenesis.

[0267] Angiogenesis, or neovascularization, is the formation of new capillaries from existing blood vessels. In adult organisms this process is typically controlled and short-lived, for example in wound repair and regeneration. However, aberrant capillary growth can occur and this uncontrolled growth plays a causal and/or supportive role in many pathologic conditions such as tumor growth and metastasis. In the context of this invention "aberrant angiogenesis" refers to unwanted or uncontrolled angiogenesis. Angiogenesis inhibitors are being evaluated for use as antitumor drugs. Other diseases and conditions associated with angiogenesis include arthritis, cardiovascular diseases, skin conditions (e.g., psoriasis), and aberrant wound healing. Aberrant angiogenesis can also occur in the eye, causing loss of vision. Examples of ocular conditions involving aberrant angiogenesis include macular degeneration, diabetic retinopathy, diabetic macular edema and retinopathy of prematurity.

[0268] The tube formation assay is performed using an in vitro Angiogenesis Assay Kit (Chemicon International, Temecula, Calif.), or growth factor reduced Matrigel (BD Biosciences, Bedford, Mass.). HUVECs were plated at 4000 cells/well in 96-well plates. One day later, cells were transfected with antisense and control oligonucleotides according to standard published procedures (Monia et al., (1993) J Biol. Chem. 1993 Jul. 5; 268(19):14514-22) using 75 nM oligonucleotide in lipofectin (Gibco, Grand Island, N.Y.). Approx-

mately fifty hours post-transfection, cells were transferred to 96-well plates coated with ECMatrix™ (Chemicon International) or growth factor depleted Matrigel. Under these conditions, untreated HUVECs form tube-like structures. After an overnight incubation at 37° C., treated and untreated cells were inspected by light microscopy. Individual wells were assigned discrete scores from 1 to 5 depending on the extent of tube formation. A score of 1 refers to a well with no tube formation while a score of 5 is given to wells where all cells are forming an extensive tubular network.

[0269] ISIS 29848 is a control oligonucleotide containing an equal mixture of the bases A, C, G and T at every position. ISIS 175510 (TGAGCTGTCTGTGATCCAGC; SEQ ID NO: 184) is targeted to HIF1 α ; ISIS 222035 (GCGCTGCTCCCAAGAACTCT; SEQ ID NO: 185) is targeted to HIF2 α . ISIS 298697 (TCCTCATGGTCACATGGATG; SEQ ID NO: 186) is a cross-HIF1 α /HIF2 α oligonucleotide having perfect complementarity to HIF1 α target and imperfect complementarity (and thus less inhibitory effect) for HIF2 α ; ISIS 311082 (SEQ ID NO: 30) is targeted to HIF1-beta.

TABLE 13

Effect of antisense oligonucleotides on angiogenic tube formation		
ISIS #	Target	Score
Lipid control	N/A	4.7
29848	Control	4.7
175510	HIF1 α	2.0
222035	HIF2 α	1.0
298697	HIF1 α /2 α	3.0
311082	HIF1-beta	2.0

[0270] As calculated from the assigned discrete scores, the results demonstrate that HUVEC tube formation is inhibited by treatment with antisense oligonucleotides targeting the Hif family. Thus, a reduction in HIF1-beta expression results in inhibition of angiogenic processes.

Example 28

HIF1-Beta Antisense Compounds in an Animal Model of Ocular Neovascularization

[0271] A pig model of ocular neovascularization, the branch retinal vein occlusion (BVO) model, is used to study ocular neovascularization. Male farm pigs (8-10 kg) are subjected to branch retinal vein occlusions (BVO) by laser treatment in both eyes. The extent of BVO is determined by indirect ophthalmoscopy after a 2 week period. Intravitreal injections (10 μ M) of HIF1-beta antisense oligonucleotides and control oligonucleotides are started on the day of BVO induction and are repeated at weeks 2, 6 and 10 after BVO (Right eye=vehicle, Left eye=antisense oligonucleotide). Stereo fundus photography and fluorescein angiography are performed at baseline BVO and at weeks 1, 6 and 12 following intravitreal injections to measure the neovascular response. In addition, capillary gel electrophoresis analysis of the eye sections containing sclera, choroid, and the retina are performed to determine antisense concentrations, and gross and microscopic evaluations are performed to determine eye histopathology.

Example 29

Matrix Metalloproteinase Activity Assay

[0272] During angiogenesis, endothelial cells need to be able to degrade the extracellular matrix (ECM). Endothelial cells secrete matrix metalloproteinases (MMPs) in order to accomplish this degradation. HIF1-beta antisense compounds of the invention are evaluated for their effects on MMP activity in HUVECs. MMP activity is measured using the EnzChek Gelatinase/Collagenase Assay Kit (Molecular Probes, Eugene, Oreg.). In this assay, HUVECs are plated at approximately 4000 cells per well in 96-well plates and transfected one day later. A 20-nucleotide oligomeric compound with a randomized sequence is used as a negative control. An oligomeric compound targeted to integrin β 3 is known to inhibit MMP activity and is used as a positive control.

[0273] Cells are transfected as described herein. Antisense compounds are mixed with LIPOFECTIN™ in Opti-MEM to achieve a final concentration of 75 nM of antisense compound and 2.25 μ g/mL LIPOFECTIN™. Antisense compounds of the invention and the positive control are tested in triplicate, and the negative control is tested in up to six replicates. Untreated control cells received LIPOFECTIN™ in Opti-MEM only.

[0274] Approximately 50 hours after transfection, a p-aminophenylmercuric acetate (APMA, Sigma-Aldrich, St. Louis, Mo.) solution is added to each well of a Corning-Costar 96-well clear bottom plate (VWR International, Brisbane, Calif.). The APMA solution is used to promote cleavage of inactive MMP precursor proteins. Medium above the HUVECs is then transferred to the wells in the 96-well plate. After approximately 30 minutes, the quenched, fluorogenic MMP cleavage substrate is added, and baseline fluorescence is read immediately at 485 nm excitation/530 nm emission. Following an overnight incubation at 37° C. in the dark, plates are read again to determine the amount of fluorescence, which corresponds to MMP activity. Total protein from HUVEC lysates is used to normalize the readings, and MMP activity from cells treated with antisense compounds is normalized to that of untreated control cells. MMP activities above or below 100% are considered to indicate a stimulation or inhibition of MMP activity, respectively. HIF1-beta antisense compounds resulting in a decrease in MMP activity are candidate therapeutic agents for the inhibition of angiogenesis where such activity is desired, for example, in the treatment of cancer, diabetic retinopathy, cardiovascular disease, rheumatoid arthritis and psoriasis.

[0275] Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each of the patents, applications, printed publications, and other published documents mentioned or referred to in this specification are herein incorporated by reference in their entirety. Those skilled in the art will appreciate that numerous changes and modifications may be made to the embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

<160> NUMBER OF SEQ ID NOS: 190

```
<210> SEQ ID NO 1
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound
```

<400> SEQUENCE: 1

tccgtcatcg ctctcaggg 20

```
<210> SEQ ID NO 2
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound
```

<400> SEQUENCE: 2

gtgcgcgcga gcccgaaatc 20

```
<210> SEQ ID NO 3
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound
```

<400> SEQUENCE: 3

atgcattctg cccccaagga 20

```
<210> SEQ ID NO 4
<211> LENGTH: 4504
<212> TYPE: DNA
<213> ORGANISM: H. sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (175)...(2542)
```

<400> SEQUENCE: 4

agcgggggat gctgggggct gctgaagccg ccatcttgga ttccgcggta gcggaggcgg 60

cggtcaggcg ccgcttctgg ggagtggcct ttcttttccc ctccctcccg gttcgggtggc 120

ggcggtcct ccactgggg ggggggtggc gcggcggcgg tggcatctgc ggc atg 177
Met
1

gcg gcg act act gcc aac ccc gaa atg aca tca gat gta cca tca ctg 225
Ala Ala Thr Thr Ala Asn Pro Glu Met Thr Ser Asp Val Pro Ser Leu
5 10 15

ggt cca gcc att gcc tct gga aac tct gga cct gga att caa ggt gga 273
Gly Pro Ala Ile Ala Ser Gly Asn Ser Gly Pro Gly Ile Gln Gly Gly

gga gcc att gtc cag agg gct att aag cgg cga cca ggg ctg gat ttt 321
Gly Ala Ile Val Gln Arg Ala Ile Lys Arg Arg Pro Gly Leu Asp Phe
35 40 45

gat gat gat gga gaa ggg aac agt aaa ttt ttg agg tgt gat gat gat 369
Asp Asp Asp Gly Glu Gly Asn Ser Lys Phe Leu Arg Cys Asp Asp Asp
50 55 60 65

caq atg tct aac gat aaq gaq cgg ttt gcc aag tcg gat gat gaq cac 417

-continued

Gln	Met	Ser	Asn	Asp	Lys	Glu	Arg	Phe	Ala	Arg	Ser	Asp	Asp	Glu	His	
			70						75					80		
ctc	tgc	gga	taa	aga	gag	act	tgc	cag	gga	aaa	tca	cag	tga	aat	tga	465
Leu	Cys	Gly	*	Arg	Glu	Thr	Cys	Gln	Gly	Lys	Ser	Gln	*	Asn	*	
			85						90							
acg	gcg	gcg	acg	gaa	caa	gat	gac	agc	cta	cat	cac	aga	act	gtc	aga	513
Thr	Ala	Ala	Thr	Glu	Gln	Asp	Asp	Ser	Leu	His	His	Arg	Thr	Val	Arg	
95				100					105					110		
tat	ggc	acc	cac	ctg	tag	tgc	cct	ggc	tcg	aaa	acc	aga	caa	gct	aac	561
Tyr	Gly	Thr	His	Leu	*	Cys	Pro	Gly	Ser	Lys	Thr	Arg	Gln	Ala	Asn	
			115						120					125		
cat	ctt	acg	cat	ggc	agt	ttc	tca	cat	gaa	gtc	ctt	gcg	ggg	aac	tgg	609
His	Leu	Thr	His	Gly	Ser	Phe	Ser	His	Glu	Val	Leu	Ala	Gly	Asn	Trp	
			130						135					140		
caa	cac	atc	cac	tga	tgg	ctc	cta	taa	gcc	gtc	ttt	cct	cac	tga	tca	657
Gln	His	Ile	His	*	Trp	Leu	Leu	*	Ala	Val	Phe	Pro	His	*	Ser	
			145						150							
gga	act	gaa	aca	ttt	gat	ctt	gga	ggc	agc	aga	tgg	ctt	tct	gtt	tat	705
Gly	Thr	Glu	Thr	Phe	Asp	Leu	Gly	Gly	Ser	Arg	Trp	Leu	Ser	Val	Tyr	
155				160					165					170		
tgt	ctc	atg	tga	gac	agg	cag	ggc	ggt	gta	tgt	gtc	tga	ctc	cgt	gac	753
Cys	Leu	Met	*	Asp	Arg	Gln	Gly	Gly	Val	Cys	Val	*	Leu	Arg	Asp	
				175					180							
tcc	tgt	ttt	gaa	cca	gcc	aca	gtc	tga	atg	gtt	tgg	cag	cac	act	cta	801
Ser	Cys	Phe	Glu	Pro	Ala	Thr	Val	*	Met	Val	Trp	Gln	His	Thr	Leu	
185				190							195					
tga	tca	ggc	gca	ccc	aga	tga	tgt	gga	taa	act	tcg	tga	gca	gct	ttc	849
*	Ser	Gly	Ala	Pro	Arg	*	Cys	Gly	*	Thr	Ser	*	Ala	Ala	Phe	
200				205									210			
cac	ttc	aga	aaa	tgc	cct	gac	agg	gcg	tat	cct	gga	tct	aaa	gac	tgg	897
His	Phe	Arg	Lys	Cys	Pro	Asp	Arg	Ala	Tyr	Pro	Gly	Ser	Lys	Asp	Trp	
			215					220					225			
aac	agt	gaa	aaa	gga	agg	tca	gca	gtc	ttc	cat	gag	aat	gtg	tat	ggg	945
Asn	Ser	Glu	Lys	Gly	Arg	Ser	Ala	Val	Phe	His	Glu	Asn	Val	Tyr	Gly	
		230				235						240				
ctc	aag	gag	atc	gtt	tat	ttg	ccg	aat	gag	gtg	tgg	cag	tag	ctc	tgt	993
Leu	Lys	Glu	Ile	Val	Tyr	Leu	Pro	Asn	Glu	Val	Trp	Gln	*	Leu	Cys	
245				250					255							
gga	ccc	agt	ttc	tgt	gaa	tag	gct	gag	ctt	tgt	gag	gaa	cag	atg	cag	1041
Gly	Pro	Ser	Phe	Cys	Glu	*	Ala	Glu	Leu	Cys	Glu	Glu	Gln	Met	Gln	
260				265							270					
gaa	tgg	act	tgg	ctc	tgt	aaa	gga	tgg	gga	acc	tca	ctt	cgt	ggt	ggt	1089
Glu	Trp	Thr	Trp	Leu	Cys	Lys	Gly	Trp	Gly	Thr	Ser	Leu	Arg	Gly	Gly	
275				280							285					
cca	ctg	cac	agg	cta	cat	caa	ggc	ctg	gcc	ccc	agc	agg	tgt	ttc	cct	1137
Pro	Leu	His	Arg	Leu	His	Gln	Gly	Leu	Ala	Pro	Ser	Arg	Cys	Phe	Pro	
290				295					300					305		
ccc	aga	tga	tga	ccc	aga	ggc	tgg	cca	ggg	aag	caa	ggt	ttg	cct	agt	1185
Pro	Arg	*	*	Pro	Arg	Gly	Trp	Pro	Gly	Lys	Gln	Val	Leu	Pro	Ser	
				310							315					
ggc	cat	tgg	cag	att	gca	ggt	aac	tag	ttc	tcc	caa	ctg	tac	aga	cat	1233
Gly	His	Trp	Gln	Ile	Ala	Gly	Asn	*	Phe	Ser	Gln	Leu	Tyr	Arg	His	
320				325							330					
gag	taa	tgt	ttg	tca	acc	aac	aga	gtt	cat	ctc	ccg	aca	caa	cat	tga	1281
Glu	*	Cys	Leu	Ser	Thr	Asn	Arg	Val	His	Leu	Pro	Thr	Gln	His	*	
335				340							345					
ggg	tat	ctt	cac	ttt	tgt	gga	tca	ccg	ctg	tgt	ggc	tac	tgt	tgg	cta	1329

-continued

Gly	Tyr	Leu	His	Phe	Cys	Gly	Ser	Pro	Leu	Cys	Gly	Tyr	Cys	Trp	Leu	
350						355					360					
cca	gcc	aca	gga	act	ctt	agg	aaa	gaa	tat	tgt	aga	att	ctg	tca	tcc	1377
Pro	Ala	Thr	Gly	Thr	Leu	Arg	Lys	Glu	Tyr	Cys	Arg	Ile	Leu	Ser	Ser	
365					370					375					380	
tga	aga	cca	gca	gct	tct	aag	aga	cag	ctt	cca	aca	ggg	agt	gaa	att	1425
* Arg	Pro	Ala	Ala	Ser	Lys	Arg	Gln	Leu	Pro	Thr	Gly	Ser	Glu	Ile		
				385					390					395		
aaa	agg	cca	agt	gct	gtc	tgt	cat	gtt	ccg	gtt	ccg	gtc	taa	gaa	cca	1473
Lys	Arg	Pro	Ser	Ala	Val	Cys	His	Val	Pro	Val	Pro	Val	*	Glu	Pro	
				400					405					410		
aga	atg	gct	ctg	gat	gag	aac	cag	ctc	ctt	tac	ttt	cca	gaa	ccc	tta	1521
Arg	Met	Ala	Leu	Asp	Glu	Asn	Gln	Leu	Leu	Tyr	Phe	Pro	Glu	Pro	Leu	
				415					420					425		
ctc	aga	tga	aat	tga	gta	cat	cat	ctg	tac	caa	cac	caa	tgt	gaa	gaa	1569
Leu	Arg	*	Asn	*	Val	His	His	Leu	Tyr	Gln	His	Gln	Cys	Glu	Glu	
				430					435					440		
ctc	tag	cca	aga	acc	acg	gcc	tac	act	ctc	caa	cac	aat	cca	gag	gcc	1617
Leu	*	Pro	Arg	Thr	Thr	Ala	Tyr	Thr	Leu	Gln	His	Asn	Pro	Glu	Ala	
				445					450					455		
aca	act	agg	tcc	cac	agc	taa	ttt	acc	cct	gga	gat	ggg	ctc	agg	aca	1665
Thr	Thr	Arg	Ser	His	Ser	*	Phe	Thr	Pro	Gly	Asp	Gly	Leu	Arg	Thr	
				460					465					470		
gct	ggc	acc	cag	gca	gca	gca	aca	gca	aac	aga	att	gga	cat	ggg	acc	1713
Ala	Gly	Thr	Gln	Ala	Ala	Ala	Thr	Ala	Asn	Arg	Ile	Gly	His	Gly	Thr	
				475					480					485		
agg	aag	aga	tgg	act	ggc	cag	cta	caa	tca	ttc	cca	ggg	ggg	tca	gcc	1761
Arg	Lys	Arg	Trp	Thr	Gly	Gln	Leu	Gln	Ser	Phe	Pro	Gly	Gly	Ser	Ala	
			490					495						500		
tgt	gac	aac	cac	agg	acc	aga	aca	cag	caa	gcc	cct	tga	gaa	gtc	aga	1809
Cys	Asp	Asn	His	Arg	Thr	Arg	Thr	Gln	Gln	Ala	Pro	*	Glu	Val	Arg	
		505					510						515			
tgg	ttt	att	tgc	cca	gga	tag	aga	tcc	aag	att	ttc	aga	aat	cta	tca	1857
Trp	Phe	Ile	Cys	Pro	Gly	*	Arg	Ser	Lys	Ile	Phe	Arg	Asn	Leu	Ser	
		520						525					530			
caa	cat	caa	tgc	gga	tca	gag	taa	agg	cat	ctc	ctc	cag	cac	tgt	ccc	1905
Gln	His	Gln	Cys	Gly	Ser	Glu	*	Arg	His	Leu	Leu	Gln	His	Cys	Pro	
		535						540					545			
tgc	cac	cca	aca	gct	att	ctc	cca	ggg	caa	cac	att	ccc	tcc	tac	ccc	1953
Cys	His	Pro	Thr	Ala	Ile	Leu	Pro	Gly	Gln	His	Ile	Pro	Ser	Tyr	Pro	
		550					555					560				
ccg	gcc	ggc	aga	gaa	ttt	cag	gaa	tag	tgg	tct	agc	ccc	tcc	tgt	aac	2001
Pro	Ala	Gly	Arg	Glu	Phe	Gln	Glu	*	Trp	Ser	Ser	Pro	Ser	Cys	Asn	
		565				570						575				
cat	tgt	cca	gcc	atc	agc	ttc	tgc	agg	aca	gat	gtt	ggc	cca	gat	ttc	2049
His	Cys	Pro	Ala	Ile	Ser	Phe	Cys	Arg	Thr	Asp	Val	Gly	Pro	Asp	Phe	
		580				585					590					
ccg	cca	ctc	caa	ccc	cac	cca	agg	agc	aac	ccc	aac	ttg	gac	ccc	tac	2097
Pro	Pro	Leu	Gln	Pro	His	Pro	Arg	Ser	Asn	Pro	Asn	Leu	Asp	Pro	Tyr	
		595			600				605					610		
tac	ccg	ctc	agg	ctt	ttc	tgc	cca	gca	ggg	ggc	tac	cca	ggc	tac	tgc	2145
Tyr	Pro	Leu	Arg	Leu	Phe	Cys	Pro	Ala	Gly	Gly	Tyr	Pro	Gly	Tyr	Cys	
				615					620					625		
taa	gac	tcg	tac	ttc	cca	gtt	tgg	tgt	ggg	cag	ctt	tca	gac	tcc	atc	2193
*	Asp	Ser	Tyr	Phe	Pro	Val	Trp	Cys	Gly	Gln	Leu	Ser	Asp	Ser	Ile	
				630				635						640		
ctc	ctt	cag	ctc	cat	gtc	cct	ccc	tgg	tgc	ccc	aac	tgc	atc	gcc	tgg	2241

-continued

tgcaagactg agttaatgag aagatatatt aaatgtagtc ataggggact gaggagcaag	4022
ggtaggccttg aagaggccaa aggaatgtcc atttgctgag tttcccttcc ttatgtctcc	4082
agctcgggtgc caggtagtgg agtaaaaaag gagacagttt atttttttat tctatgtgca	4142
cacttacagt atacatatat atttatatca caatttacga aacccaaaaag ttgagtttcc	4202
aatggaaccc ttgtttttta ataatcgact ttttaaatgt gatcaagact ataatatgt	4262
acagttatta tagggcctttt ggggaagggg aggatagcga gaagatgctc tgggggtttt	4322
gtttttgctt ttccttcagg gttttatttt tgactgtttt gttttcttgt tggccatttc	4382
tgtattgctg gcatctgtgc taagctttac agtggcaaaa ataatgacat gtagcaaaga	4442
ttttcaaaca aaatatTTTT tccttttgta aaaaaaaaaa aaaaagaaaa aaaaaaaaaa	4502
aa	4504

<210> SEQ ID NO 5
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR Primer

<400> SEQUENCE: 5

agcagagggt gtgggtgtct	20
-----------------------	----

<210> SEQ ID NO 6
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR Primer

<400> SEQUENCE: 6

tggcggttgt tgaacatgtt	20
-----------------------	----

<210> SEQ ID NO 7
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR Probe

<400> SEQUENCE: 7

ccagcagcct catcatcggt ca	22
--------------------------	----

<210> SEQ ID NO 8
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR Primer

<400> SEQUENCE: 8

gaaggtgaag gtcggagtc	19
----------------------	----

<210> SEQ ID NO 9
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR Primer

-continued

<400> SEQUENCE: 9

gaagatggtg atgggatttc

20

<210> SEQ ID NO 10

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR Probe

<400> SEQUENCE: 10

caagcttccc gttctcagcc

20

<210> SEQ ID NO 11

<211> LENGTH: 2691

<212> TYPE: DNA

<213> ORGANISM: M. musculus

<220> FEATURE:

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (110)...(2485)

<400> SEQUENCE: 11

gcggcggtaa ggtgctaata ctgcggagtg gctcttcct cccctcccc agtcggtgg

60

cggtgcccc tcccaccgag ggtggcgag ggacggtgcc atctcgacc atg gcg gcg
Met Ala Ala
1

118

act aca gct aac cca gaa atg aca tca gat gta cca tcg ctg ggt ccc
Thr Thr Ala Asn Pro Glu Met Thr Ser Asp Val Pro Ser Leu Gly Pro
5 10 15

166

acc att gct tct gga aac cct gga cct ggg att caa ggt gga gga gct
Thr Ile Ala Ser Gly Asn Pro Gly Pro Gly Ile Gln Gly Gly Gly Ala
20 25 30 35

214

gtt gta cag agg gct att aag cga cgg tca ggg ctg gat ttt gat gat
Val Val Gln Arg Ala Ile Lys Arg Arg Ser Gly Leu Asp Phe Asp Asp
40 45 50

262

gaa gta gaa gtg aac act aaa ttt ttg aga tgc gat gat gac cag atg
Glu Val Glu Val Asn Thr Lys Phe Leu Arg Cys Asp Asp Asp Gln Met
55 60 65

310

tgt aat gac aaa gag cgg ttt gcc agg tcg gat gat gag cag agc tct
Cys Asn Asp Lys Glu Arg Phe Ala Arg Ser Asp Asp Glu Gln Ser Ser
70 75 80

358

gcg gat aaa gag aga ctt gcc agg gaa aat cat agt gaa ata gaa cgg
Ala Asp Lys Glu Arg Leu Ala Arg Glu Asn His Ser Glu Ile Glu Arg
85 90 95

406

cgg cga cgg aac aag atg aca gct tac atc aca gaa ctg tca gac atg
Arg Arg Arg Asn Lys Met Thr Ala Tyr Ile Thr Glu Leu Ser Asp Met
100 105 110 115

454

gta cct aca tgt agt gcc ctg gct cga aaa cca gac aag cta acc atc
Val Pro Thr Cys Ser Ala Leu Ala Arg Lys Pro Asp Lys Leu Thr Ile
120 125 130

502

tta cgc atg gcc gtt tct cac atg aag tcc ttg agg gga act ggc aac
Leu Arg Met Ala Val Ser His Met Lys Ser Leu Arg Gly Thr Gly Asn
135 140 145

550

aca tct act gat ggc tcc tac aag cca tct ttc ctc act gat cag gaa
Thr Ser Thr Asp Gly Ser Tyr Lys Pro Ser Phe Leu Thr Asp Gln Glu
150 155 160

598

ctg aaa cat ttg atc ttg gag gca gca gat ggc ttt ctg ttt att gtc
Leu Lys His Leu Ile Leu Glu Ala Ala Asp Gly Phe Leu Phe Ile Val

646

-continued

165	170	175	
tcc tgt gag act gga cgg gtg gtg tat gtc tct gac tca gtg act ccc			694
Ser Cys Glu Thr Gly Arg Val Val Tyr Val Ser Asp Ser Val Thr Pro			
180	185	190	195
ggt ttg aac cag cca cag tct gaa tgg ttc ggg agc aca ctg tat gat			742
Val Leu Asn Gln Pro Gln Ser Glu Trp Phe Gly Ser Thr Leu Tyr Asp			
	200	205	210
cag gtg cac cca gat gat gtg gat aaa ctt cga gag cag ctc tct aca			790
Gln Val His Pro Asp Asp Val Asp Lys Leu Arg Glu Gln Leu Ser Thr			
	215	220	225
tca gaa aat gcc cta aca ggg cgg gtc ctg gat ctg aag act gga aca			838
Ser Glu Asn Ala Leu Thr Gly Arg Val Leu Asp Leu Lys Thr Gly Thr			
	230	235	240
gtg aaa aag gaa ggc cag cag tct tcc atg agg atg tgc atg ggc tca			886
Val Lys Lys Glu Gly Gln Gln Ser Ser Met Arg Met Cys Met Gly Ser			
	245	250	255
cga agg tgc ttc atc tgc cgc atg agg tgt ggt act agc tcc gtg gac			934
Arg Arg Ser Phe Ile Cys Arg Met Arg Cys Gly Thr Ser Ser Val Asp			
	260	265	270
cct gtt tcc atg aat aga ctg agc ttt ttg agg aac aga tgc agg aat			982
Pro Val Ser Met Asn Arg Leu Ser Phe Leu Arg Asn Arg Cys Arg Asn			
	280	285	290
ggg ctt ggc tct gtg aag gaa gga gaa cct cac ttt gtg gta gtc cac			1030
Gly Leu Gly Ser Val Lys Glu Gly Glu Pro His Phe Val Val Val His			
	295	300	305
tgc aca ggc tac atc aag gcc tgg cca cca gca ggt gtc tcc ctc cca			1078
Cys Thr Gly Tyr Ile Lys Ala Trp Pro Pro Ala Gly Val Ser Leu Pro			
	310	315	320
gat gat gac cca gag gct ggc cag ggg agc aaa ttc tgc cta gtg gcc			1126
Asp Asp Asp Pro Glu Ala Gly Gln Gly Ser Lys Phe Cys Leu Val Ala			
	325	330	335
att ggc agg ctg cag gta act agt tct ccc aac tgt aca gac atg agt			1174
Ile Gly Arg Leu Gln Val Thr Ser Ser Pro Asn Cys Thr Asp Met Ser			
	340	345	350
aac att tgt cag cca aca gag ttc atc tcc cga cac aac att gaa ggg			1222
Asn Ile Cys Gln Pro Thr Glu Phe Ile Ser Arg His Asn Ile Glu Gly			
	360	365	370
ata ttc act ttt gta gac cat cgt tgt gtg gct act gtt ggc tac cag			1270
Ile Phe Thr Phe Val Asp His Arg Cys Val Ala Thr Val Gly Tyr Gln			
	375	380	385
cca cag gag ctc tta ggg aag aat att gta gaa ttt tgt cat cct gaa			1318
Pro Gln Glu Leu Leu Gly Lys Asn Ile Val Glu Phe Cys His Pro Glu			
	390	395	400
gac caa caa ctt cta aga gac agc ttt cag cag gtg gtg aaa tta aaa			1366
Asp Gln Gln Leu Leu Arg Asp Ser Phe Gln Gln Val Val Lys Leu Lys			
	405	410	415
ggt cag gtg ctg tcc gtc atg ttc cga ttc cga tct aag acc cga gaa			1414
Gly Gln Val Leu Ser Val Met Phe Arg Phe Arg Ser Lys Thr Arg Glu			
	420	425	430
tgg ctg tgg atg aga acg agc tcc ttt acc ttc caa aac cct tat tca			1462
Trp Leu Trp Met Arg Thr Ser Ser Phe Thr Phe Gln Asn Pro Tyr Ser			
	440	445	450
gat gaa att gag tat att atc tgc acc aac acc aat gtg aag aac tct			1510
Asp Glu Ile Glu Tyr Ile Ile Cys Thr Asn Thr Asn Val Lys Asn Ser			
	455	460	465
agc cag gaa cca cgg cct aca ctg tcc aac acc atc cca agg tca cag			1558
Ser Gln Glu Pro Arg Pro Thr Leu Ser Asn Thr Ile Pro Arg Ser Gln			

-continued

470	475	480	
cta ggt ccg aca gcc aat tta tcc cta gag atg ggt aca ggg cag ctg Leu Gly Pro Thr Ala Asn Leu Ser Leu Glu Met Gly Thr Gly Gln Leu 485 490 495			1606
cca tcc agg cag cag cag cag cag cac aca gaa ctg gat atg gta cca Pro Ser Arg Gln Gln Gln Gln Gln His Thr Glu Leu Asp Met Val Pro 500 505 510 515			1654
gga aga gat ggg ctg gcc agc tat aat cat tcc cag gtt tct gtc cag Gly Arg Asp Gly Leu Ala Ser Tyr Asn His Ser Gln Val Ser Val Gln 520 525 530			1702
cct gtg gca agt gca gga tca gaa cac agc aag ccc ctt gag aag tca Pro Val Ala Ser Ala Gly Ser Glu His Ser Lys Pro Leu Glu Lys Ser 535 540 545			1750
gaa ggt ctc ttt gca cag gac aga gat cca agg ttt cca gaa atc tat Glu Gly Leu Phe Ala Gln Asp Arg Asp Pro Arg Phe Pro Glu Ile Tyr 550 555 560			1798
ccc agc atc act gca gat cag agt aaa ggc atc tcc tcc agc act gtc Pro Ser Ile Thr Ala Asp Gln Ser Lys Gly Ile Ser Ser Ser Thr Val 565 570 575			1846
cct gcc acc caa cag ctg ttc tcc cag ggc agc tca ttc cct cct aac Pro Ala Thr Gln Gln Leu Phe Ser Gln Gly Ser Ser Phe Pro Pro Asn 580 585 590 595			1894
ccc cgg ccg gca gag aat ttc agg aat agt ggt ctt acc cct cct gta Pro Arg Pro Ala Glu Asn Phe Arg Asn Ser Gly Leu Thr Pro Pro Val 600 605 610			1942
acc att gtc cag cca tca tct tct gca ggg cag ata ctg gcc cag att Thr Ile Val Gln Pro Ser Ser Ser Ala Gly Gln Ile Leu Ala Gln Ile 615 620 625			1990
tca cgt cac tcc aac cct gcc cag gga tca gcg ccg acc tgg acc tct Ser Arg His Ser Asn Pro Ala Gln Gly Ser Ala Pro Thr Trp Thr Ser 630 635 640			2038
agc tcc cgc cca ggc ttt gcc gcc cag cag gtg ccc acc cag gct aca Ser Ser Arg Pro Gly Phe Ala Ala Gln Gln Val Pro Thr Gln Ala Thr 645 650 655			2086
gcc aag act cgt tct tcc caa ttt ggt gtg aac aac ttt cag act tct Ala Lys Thr Arg Ser Ser Gln Phe Gly Val Asn Asn Phe Gln Thr Ser 660 665 670 675			2134
tcc tcc ttc agt gct atg tct ctt ccg ggt gct ccc act gcc tca tct Ser Ser Phe Ser Ala Met Ser Leu Pro Gly Ala Pro Thr Ala Ser Ser 680 685 690			2182
ggt act gct gcc tac cct gct ctc ccc aac cgt ggc tcc aac ttt cct Gly Thr Ala Ala Tyr Pro Ala Leu Pro Asn Arg Gly Ser Asn Phe Pro 695 700 705			2230
cct gag act gga cag acc aca gga cag ttc cag gcc cgg aca gca gag Pro Glu Thr Gly Gln Thr Thr Gln Phe Gln Ala Arg Thr Ala Glu 710 715 720			2278
ggc gtg ggt gtc tgg cca cag tgg cag ggc cag cag ccc cat cat cgg Gly Val Gly Val Trp Pro Gln Trp Gln Gly Gln Gln Pro His His Arg 725 730 735			2326
tct agt tcc agt gag cag cat gtt cag cag aca caa gca caa gca cct Ser Ser Ser Ser Glu Gln His Val Gln Gln Thr Gln Ala Gln Ala Pro 740 745 750 755			2374
agc cag cct gag gtc ttt caa gaa atg ctg tcc atg ctg gga gac caa Ser Gln Pro Glu Val Phe Gln Glu Met Leu Ser Met Leu Gly Asp Gln 760 765 770			2422
agc aac acc tac aac aat gaa gaa ttt cct gat cta act atg ttt ccc Ser Asn Thr Tyr Asn Asn Glu Glu Phe Pro Asp Leu Thr Met Phe Pro			2470

-continued

775	780	785	
ccc ttt tcc gaa tag aactattggg gtgaggataa ggggtggggg aaatcactgt			2525
Pro Phe Ser Glu			
790			
ttgttttttaa aagcaaatct ttgttaaaca gaataaaaagt tcctctccct tcccttccct			2585
caccctgat atgtaccctt tccaccctt gacttgctga agaaacgtta tagaagaaat			2645
taaatgaatt tcccaggcaa aaaaaaaaaa aaaaaaaaaa aaaaaa			2691
<210> SEQ ID NO 12 <211> LENGTH: 20 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR Primer			
<400> SEQUENCE: 12			
ggcatctcct ccagcactgt			20
<210> SEQ ID NO 13 <211> LENGTH: 28 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR Primer			
<400> SEQUENCE: 13			
ggtaagacca ctattctga aattctct			28
<210> SEQ ID NO 14 <211> LENGTH: 20 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR Probe			
<400> SEQUENCE: 14			
tccctcttaa cccccggcgcg			20
<210> SEQ ID NO 15 <211> LENGTH: 20 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR Primer			
<400> SEQUENCE: 15			
ggcaaattca acggcacagt			20
<210> SEQ ID NO 16 <211> LENGTH: 20 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: PCR Primer			
<400> SEQUENCE: 16			
gggtctcgcct cctggaagat			20
<210> SEQ ID NO 17 <211> LENGTH: 27 <212> TYPE: DNA			

-continued

<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PCR Probe

<400> SEQUENCE: 17

aaggccgaga atgggaagct tgtcatc 27

<210> SEQ ID NO 18
 <211> LENGTH: 67787
 <212> TYPE: DNA
 <213> ORGANISM: *H. sapiens*

<400> SEQUENCE: 18

ttagtagaga cggggtttcg ccatgttggc caggctggtt tcgaaccctt ggccacaggt 60
 gatccggccg cctcggcctc ccaaagtgtc gggattacag acgcgagcca ccgcgcccag 120
 cctaaaatac ccattttaat tgcatttcaa tgacgttact cggtcattga cctcttacgc 180
 aaggaggggc agattaggga gacagctgga cttcttctc gcctccctt cactggactg 240
 gctggcgca gtagtagccc tgccttgga cgatttgga ttttcattgg tcaatttttc 300
 ttaggaggct ggccgtgtgt tgactccgc tactatatag gcgggtctc ccgcgcgag 360
 gggctgggat gctgggggt gctgaagcc ccatcttgga ttccgcgga gcggaggcgg 420
 cggtcaggcg ccgtcttctg ggagtggcct ttcttttccc ctccctccc gttegggtgc 480
 ggcggtcct cccactggg ggggggggtg gcgcgcgcg gtggcatctg cgcccatggc 540
 ggcgactact gccaaccgc gtgaggagac ggaggactgg ggcgcctcta aaggggaggg 600
 gccgaaggg ctgacaacta aggagacca gggctgagg gacgcagctg gagctgaagg 660
 cgccggggcg gggcggggc gcgagagac ggtgggggag cggtgacctg gggaggggccc 720
 cgatcccggt gacttggtga gactcgagta tacccaagg agcgagggg cagggtgggag 780
 ttgagggggg ctccctgtcc tgacctcgt tggagcgga gccagtgcgg ggctggccc 840
 cctcactcc tcggtcggcg tctggtctgt gatgtgttc tcttttaacc ctctgcccgc 900
 tggagccgct tgatcgcaa aactgtagg agagtgtct gggttacttt aagagtagtt 960
 tggattcata aacctggac cactctgct ttagttgag gcgttgcttc caaacattta 1020
 aaggtttaga ttttaattta aaaaataaaa aatggacatt ctttgatata tacgacgttt 1080
 ctttaggctg ttacctccca ccgcacccc ccgtcccggt ctccgtccc ggactatact 1140
 ttgaaactta gatcttgtgt taagagggcc ttaggtctt tgctgtctga ggcaggggt 1200
 ttgtgtaatg gttatggtc cggacaggtc ttagttcca cagcccagg tttaaatctt 1260
 gttaggccta cgtcaggca atttccaaac tcttcagaa aagtttgatt ccacaccatt 1320
 tctcaatttc aaaaaataat caaatatcaa aaaggtttg tctgtttgt ctaagagatg 1380
 gagtaggggt tagtgcatgt ctagagagat cagatcttca aattactagt ccagccctc 1440
 tttctctat gttacagtta ttcctcttga gaaggcattt cattttagg gtctagtta 1500
 tcttgagac cttggttatt cttgccaaat aaagtctatc cttttccaaa aaccaatata 1560
 tttgatagcc ttaaaaagg ccttgagata tgtgtgtgtg ttgcgtgggg cgagaattt 1620
 cttgaaaata aaacagtagg agtgattacc cccatcccca cgttgaaatt taaattagat 1680
 ttttttcat gttactgaaa ggcagtatga ttttgcaata tccagatttt gataggacag 1740
 ttgaatcact gaaatttctt ttctaccgt tttctggga tagctatttt aagaaatggt 1800

-continued

taatttgtca	cgtcattttt	ttttaatctt	ttaaattttt	tttgaaggaa	agggaggtaa	1860
aattaatcgc	aaaaattaca	ttgcaggaag	tgctgagtga	tagaataaaa	ctataaaaca	1920
ggaaaaatgc	cgttatgtca	aacctgacct	tgtagtaata	taacctatct	gtgaactatg	1980
gaataaataa	acaagatttt	taactgatca	cacattgcaa	aatacttata	taaccctagt	2040
taaattgcaa	agcattttct	ttattaagaa	gtggcctggg	taaacaagtt	ttagttcata	2100
tgtcagaagc	ttttttccag	ctgtgtgggt	ggggttgctt	tattttgttt	tgttttttga	2160
acaacagcaa	ccagaatgac	agcctcttga	ccatattttc	ataagctgat	caatatcagc	2220
ttaaacttta	gcagaaaata	gcataatgta	gtgtgtatgt	gtgtgtgcag	aatccttggt	2280
aatgaaacag	ctttgtttac	tatgctttgg	ctgcttgctt	ctgcaatttt	tagatttcct	2340
ttttcttttt	ctttgttttc	ctttctcttc	tccctctctt	cctgtccctt	ctccctcttt	2400
tttcttttgc	tacagggctt	tgctccttgc	tctgtcgcct	agtctggagt	gcagtggcaa	2460
gatcactgct	cacggcagcc	tccacctcag	gggctcaagt	gatcctctca	cgatcagcct	2520
cccgaatagc	tgggactaca	ggtgccttgc	caccatgcgc	ggttaatttt	taaatttttt	2580
tgtagagaca	gatgccttgc	tatgttgccc	atgctgatct	tgatctcctg	gtctcaagca	2640
agccttgcct	cagtctctcc	aagttgggaa	tacagatgtg	agacactttg	accagatttc	2700
ttttttgatg	ttgaaaaatt	attccatctc	ttctgactta	ttgatcccat	gttcagttca	2760
atcaaatcag	aagatatatt	ttcttttttc	ttttctccct	ttgctcttgt	atatcatgag	2820
gaagagatca	gagatacatt	gtggattttt	tcagtagcct	gttgcttttt	gggaaatgag	2880
attaatgaat	ggaggacat	aggtggaaat	gtactgtgct	tagtgaaagt	aaatgttttc	2940
aggtcagaat	tctttgctac	actgtcatat	cttctttcct	tagagccatt	ttaaggacta	3000
gggacaccat	gcctattttt	ttgagttttt	tctactttgt	atttttgctg	gagtactaat	3060
tttttttttt	tttttttttt	ttttacaatt	cttggttagtt	ttgtcaagat	tttaaaaaat	3120
atttcactct	ttaaccttca	cttcagttaa	tcctttttta	aaataatact	tattttttatt	3180
tttcagacag	gttcttgcct	tgtctccag	actgtagtgc	aatgggttaa	tcacagctca	3240
ctgtagcctt	gaactcctga	gctcaagtga	tcttcccacc	tcagcctcct	gagtatctgg	3300
gtctacagac	acacaccacc	acacctggat	acatttttta	actttttgta	gaaatgggat	3360
cttgctatgt	tgccaggctt	gatcttgaac	tcctgtcttc	aagcaatcct	cccaccttag	3420
cctcctaaac	tgctgggatt	ataggtgtga	gccactgacc	cggccaagtt	aatccttagg	3480
gttagtaata	gtgcttgaac	atgttaattg	tgctgggtggc	cctgcagtgt	ttttcaaggg	3540
gaccacgttc	ttctgcattt	ttcactgtgg	tgctgcatta	gaagaagagt	aaaatatggg	3600
tggtactctc	taagagtgtg	gttgaagtaa	tagttctgtg	atgatttttt	ttctcgaatt	3660
gataattctt	catattctat	cattttttac	tagttctact	tatcactggc	aagtagaact	3720
cgggtggtag	gtgggtccatg	aaacttttagg	ctgtttctta	tctatggact	agacaagttt	3780
tgttttgttt	tttttttgtt	tgtttgtttg	ttttgagaca	gagtctcact	ctgtgcacca	3840
ggctggagtg	cagtgggtgt	atcttggttc	actgcaagct	cgcctccca	ggttcacgcc	3900
attctcctgc	ctcagcctcc	cgagtagctg	ggactacagg	taccggccac	cacgccgggc	3960
taattttttt	ttttgtattt	ttagtagaga	cagggtttca	ccctgttagc	caggggtggtc	4020
tcgatctcct	gaccttgtga	tccgcctgcc	toggcctccc	aaagtgtctg	gattacaggc	4080

-continued

ttgagtcacc	gtgcccgcc	cggactagac	aagttttgag	gaacacattt	tttttcccca	4140
taggagaggg	tcttgctctg	tactgaggc	tggagtgcag	tgacacaatc	atggctcact	4200
gcagccttga	ccttctggga	gcatgtgac	ctcccacttc	agcctcctga	gtaggtggga	4260
ccacaggtgt	gcaccaccgt	ggctggctaa	ttttaaat	tttttagaga	caggtctctg	4320
ctatgttgcc	caggctggtc	tttaactcct	ggcctcaagt	gatcttcctg	cgttgggcac	4380
tccccaagag	ctgggattat	aggcatgacc	accatgccca	gccaaagggtg	aacacttttt	4440
aaattgaatg	tgtcatttgt	aatgcattgg	ctgagggaac	agttgggagg	agattaggta	4500
tttgatttac	aattccaaat	tcaaactaga	gatgttgaat	gagttttag	taagtgtagg	4560
tttttatctc	tcttgattct	ggtattctca	ttagcagaga	attctttttg	tgtattatg	4620
tacaagttac	tgtggatgaa	gaatgtagaa	ggaaaagggt	aataccgttt	gggtttgtaa	4680
ggctgtcatt	taggaagaaa	atttttttta	gctaattttc	acctatataa	cttagtttta	4740
actgcgtcaa	ttaacacaat	tcttacctgt	tacctttatt	tacctttttc	agatatggga	4800
aaataggaat	tcatgcaatg	taaagttaag	atgtcaagat	attcttttat	ggccaggtgt	4860
ggtggctcgt	gcctctaate	cctttgggag	gccgaggcag	gccgattgct	tgagcccagg	4920
aatttgagac	cagcccgga	aacgtgacga	aacccttta	ctacaaaaaa	tacaaaaaat	4980
tttcgggca	ctgtggtgca	cttctatagt	cccagctact	tgggaggtg	agatgggagt	5040
atcacctgag	cctggaaagt	tgaagctgca	gtgagctgtg	atcatgccac	tgtactccag	5100
cctgggtgtt	ggagtggag	cctgtccccc	aacaaaaaaa	gagatagtat	tttattatat	5160
tgcaaaggcc	tttttttttt	tttttttttt	tttttgagac	agggtcttac	tgtgtcgccc	5220
aggctggagt	gcaatggcgt	gatcttggt	cactgcaacc	tccgcctcct	gggttcaagc	5280
tattctcccg	cctcagcctc	cggagtagct	gggattacag	gcacctgcca	tcacgccggc	5340
taatttttta	tttttaatat	agacagggtt	tctccatgtt	ggccaggtg	gtcttgaact	5400
cctcacctca	ggtgatccgc	ccaccttggc	ctcccaaagt	gctgggatta	caggcgtgag	5460
cgcgcctgct	cgcgcgccat	ctgtttttta	gaatgctgcc	ttggccgggc	atgggtggctc	5520
atgectgtaa	tcctagcatt	ttgggaggcc	gaagtgggca	gatcacctga	ggtcaggagt	5580
tcaagaccag	cctggccaac	atggagaaac	cctgtctcta	ctaaaaatac	aaaaattagc	5640
caggcatggt	ggcaggtgcc	tgtaatccca	gctactcggg	aggctgaggc	gggagaatcg	5700
cttgaacctg	gaagggtggt	gttgacgtga	gctgagatcg	taccactgca	ctctagcctg	5760
ggcgacagag	tgagactccg	tctaaaaaaa	aaaaaaaaaa	aaaaaaaaac	acgactgcct	5820
aatatgccat	aatgacttta	gtaagtagac	atcagtgaat	cttcaggttg	gaaatatgac	5880
aacacctatc	attttacact	taaggagaca	aaccaggga	aaggagtgga	taattaagtt	5940
ccttctatat	gccaggctgc	actttcctat	ttgttgcta	atctttatgt	ctagtctgta	6000
gcaactgtct	ccaacttttc	acataaaactc	ttcaaattta	tgtcactttt	cataatttcg	6060
tcaatgtatt	ttctgttttt	aaagttttta	ttattttaga	tagtgaccgg	gtctcactat	6120
attgccccgg	ctggctctca	actcctgggc	tcaagcaatc	ctcctgcctc	ggcctcccag	6180
agtgcggggg	ttacaggtgt	gagccaccct	ctgaggccca	ttttatat	ttccctccacg	6240
ttttcattgt	agttgaatgg	acaagtaagt	ttatggattc	aacagtatac	ttagggctgg	6300
acatggtggc	tcatacctgt	aatcctagca	ctttgggagg	ctgatgtagg	tggattgctt	6360

-continued

gagcccaaaa gtttgagacc agcctgggca acgtggtgaa accccatctg tacaaaaaaa	6420
tacaaaaaat tagcaggggtg tggtagcatt ccctgtagtc ccagctacgt gggagactga	6480
gatgcgagga tgacctgagc ctgggaggtt gagctgcag tgagccatga ttgtgccact	6540
gcattcctgt ctgggtgact aggagacaga gtgagaccct gtctcaaaaa acacaacaaa	6600
accagcatac ttaggatata agttccatga gagcagaact tttgctttcc ttgtttacca	6660
gagcattgca gtgcttacag tgggtgccta gtatgttggg ttagagttca atgtatgttt	6720
gtggaataaa aatgaatgta aaaccactg ttaatatgaa atacctttga agggataaaa	6780
ctaattaagc cattgacatc atgaatttgt actaactata ataatatcta atatttatta	6840
gtaatactta ccagctgttc tcatttaatt tttataacaa tcgtattagg taagtattat	6900
tattcttgtt ttacagatga ggaaactaag gcacagagag tgaataagta acttgtctga	6960
agtcacatag ctactagaag ttagagacag aattttattg ttggcagtcc atctacacag	7020
tcacattctt taatctccaa gttatgattt tttccattgt gacttagagt caccttccta	7080
ctgaaatata gtacaatgga tatcttttga gaaggaggtg ggtggagtat tgtctttttt	7140
gtagatgaaa agggtgaaat accacattag gcagcctggg ggcaaggcat tgcttggttg	7200
gagaaccaag tgcaagggtc taaaaaagg agctagaaca gtagtttcca ggctgagtgt	7260
ggtggctcat acctgtaate tcagcacttt gagagggcag ggtgagagga ttgtttaagc	7320
ccaggagtgt gagaccagcc tgagcaatat agggagacct tgtctccaca aaaatatata	7380
taaaaaaatt agctagatgt ggtggtggat gcctatagtc ccaactactt gggaggctga	7440
ggtggtggga ggatctctga gcttgctagg tcagggtgct agtgagccat gatcatgcca	7500
ctggactcta atctggttga cagagtgcgc ccctgtctct aggaaaaaaa aaaaaaagg	7560
agtagtttcc taaaactttt tctgtaacat tctataattc ttcattttgt tttgttttgt	7620
ttttttgaga ctgagtgtcc ttctgtcacc caggctgggg tgacgtggca cgatctcagc	7680
tcactgcaag ctccgcctcc cagggttcacg ccattctcct gcctcctcct cgcgagtagc	7740
tgggactaca ggcatccacc accatgcctt gctaattttt tgtgttttta gtggagatgg	7800
ggtttcactg tgtagccag gatggcctcg atctcctgac cttgtgatcc gccacctca	7860
gcctcccaaa gtgctgggat tataggcttg agctagcgcg cccagcctaa cattctatat	7920
ttctttctcc tagttctatg tttcaattct ttaaatactt ttaagggttt ttttgagaca	7980
aggtcctgtt gtgtcagcca ggctggagtg cagtagcgtg accatagctt cctgcaacac	8040
ctccaattcc taggctcaag cgattctcac tctcagttt cctgaatagt tgggaccata	8100
ggtatgcacc atcatgcccc gctaattttt taatttttga gagacaggat ctgcgtatgt	8160
tgccagggtt ggtccttttt tttttaaatt ttattattat tttttgagac ggagtcttgc	8220
tttgtcacc aggctggagt gcagtggcgt gatctcggct cactgcaacc tctgcctccc	8280
gggtttaagc gattctcctg cctcagctc ctgtagctgg gactacagga acgtgccacc	8340
gcgctgggtt aatttttgtt tttttagtag agacggggtt tcaccatgtt ggccaggatg	8400
gtctcgatct cctgacctcg tgatctgccc acctcggcct cccaaagtgc tgggattaca	8460
ggcgtgagcc accgcgcccc gcctgcccag gctggtcttg aactactgtc ctgcagtgt	8520
cctcctgctg ttggcctccc agattgctga gattacagga atgaatcatg cactgcagct	8580
tttaggattg ttattagaat cctctacaag ttcttgatac tccataattg agcctctcct	8640

-continued

agaaacttgg	tttcagagac	actgttgcta	ggtctttatc	actgattggt	ccttctttgt	8700
cctttttgct	tatctttctg	cttggtttct	tctcttggtc	agtatgcttc	tactttttct	8760
ttctcaccct	tgaggctagg	actcttcttt	gagacagggt	cttgactcct	ttttgagaca	8820
gggtcttgct	atgttgccca	cggttggtctt	ggattcctga	gctcaaatga	tcctcccacc	8880
tctgcttcct	gagtagctgg	gattacaagt	gtacaccaca	gtgcccggct	tggggctaga	8940
actaaatagt	aaaccaagca	gtttccttca	tttcttccca	tttgcccacc	tacctgcctt	9000
tctagctgct	tgcttctcta	cttcaatttg	acattcactt	ggtacctacc	atagtctctt	9060
tccttttgta	ttagtccatt	ctcacactgc	tataaataac	tacctgagac	tgggtaattt	9120
atgaagaaaa	gagggttaat	tgactcatag	ttccgcaggc	tgtatgggag	gcagggctgg	9180
ggaggcctca	ggaaacttgg	aatcatggcg	gaaggcgaag	gggaagcaag	catgtcttca	9240
catggctggc	aggatagagg	gagagaaggg	gaagggtgcta	cacactttca	aacaaccaga	9300
tctcttgaga	actctatcat	gagagagcat	taggggaatg	gtgctaaacc	tttggaacc	9360
accctatga	tccaataacc	tcccaccaga	ctgcaccttc	aacactgggg	attacaattt	9420
gacatgatat	ttgggtggag	acacacagag	ccaaccata	tcacccttta	tttatctttt	9480
atgtataaaa	gactccaaaa	atttcattcc	tggcttctca	cataaactac	tttcttatat	9540
ttttatctat	ttaaaagata	tctctctctt	tttcttttaa	agttgagaca	gggttttact	9600
atgttgccca	ggctgggtctt	gaaatcctgg	gctcaagcat	tcctcccact	tcagcaacct	9660
gagtagctgg	actacagggt	tgtgcccattg	tgcttggtg	catctctgtt	tgaatagttt	9720
tttttttttt	taatttatag	aaatgaggte	tcactgtatt	gccagactg	gtcttgaaact	9780
gctgagctca	agtagtcccc	ccatcttggt	ctccctagta	gctgggatta	taggtgtatg	9840
acacgatgcc	cagctctatt	tgagtaatct	gttttttttt	gttggtgttg	ttttttttta	9900
agacagagtc	tttctgtggt	gcccaggctg	gagtgcagtg	gtgcgatctt	ggctcaccgc	9960
agcctccgcc	tcctagggtc	aaatgatttt	tgtgcctcag	cctctcgagt	agctgggact	10020
acagtgtgcc	accacgcctg	gctaattttt	tgtatcttta	gtagagatgg	ggtttcacca	10080
tgttgccag	gctgggtctg	aactcccgtc	ctcaagtgat	ccacctgcct	tggcctccca	10140
cagtgtctgg	attacaagtg	tgagccattg	cgcccagcct	ctatttgaat	aatctttaac	10200
atcctatata	tgtatgtact	caccagtatt	tcctttaaat	ctgctgttct	tectaccttt	10260
ctgtatcttt	catcactatc	acaattcagt	ttttcatttc	cccaggctaa	ggaactataa	10320
gtgtttggat	tttatttttt	atgtgtttat	ctgggttatt	aactcttctc	aggtcttttg	10380
cctaaatatac	gtgtgtgtgt	gtgtatatgt	atgtgtgtat	acatacatat	ataaaagtta	10440
tttaaatcaa	aactatacat	ccatatatta	atatttaaag	acttagatag	ttttataaaa	10500
tgtttgttac	aaaaaaatta	taaggaggtc	ctctgctccc	tttctctcat	ttccttctct	10560
ccagtggcat	cattttttatt	tcttttaaca	gaattctttg	tttctgttta	aataaagtgt	10620
cccagtga	gacattagtt	tccagatcaa	aggggctgtg	cacacatcaa	ggccatttat	10680
gctgaaattt	cagcatcaga	tagagaatat	cctataagct	tcagagagaa	taagattatt	10740
cacattcaaa	agattcaggt	atcagattgg	tcttttttct	cagtagtcat	gctggaaagt	10800
agaagacctt	ggaacaggct	gactgacctt	gggtggtcac	gcctgtaatc	ccagcatttt	10860
gggaggctga	ggcagggtga	tcacctgagg	tcaggagtgt	gggaccagcc	tggccaacat	10920

-continued

ggtgaaaccc	cgtctctact	aaaaatacaa	agattagttg	gacgtggtgg	tgtgtgcctg	10980
tagtaccagc	tacttgggag	gctgaggcag	gagaattgct	tgaacctggg	aagcagaggt	11040
tgacgtgagc	cgagatcacg	ccactgcaca	ccagcctggg	caaaagagcg	aagactctgt	11100
ctcaaaaaaa	aaaaaaaaaa	ctttggagta	atgccttcaa	aattctgagg	gaaaataaat	11160
tctaatttag	aattccatag	ctaggcaaac	tatcaattag	tgaatagaa	gaaatatatt	11220
catacatcca	aggcattttc	tacacccttt	caggaatcca	ctagaagata	ggctctacca	11280
gtaggagata	gtaaaccaag	aaagtggaga	tacgaaatat	aggaaatagg	cagtataaca	11340
cagaagaaaa	atgaagcatg	tagtatgcat	acattggtgt	tagttttcct	gttttcagta	11400
cgggtccctc	actttcacct	ttacgtcgtg	ttcactagac	tgtaaagcct	ttgatttata	11460
ctctccagag	agtaaatctg	tcttttgaca	gaatggagag	gggtagtgtc	cttggttaga	11520
aggaatagag	aaaaggatct	aggaatccat	ctctgtagta	aacagatgct	gaactaattc	11580
tccttatatt	catttcattc	accctaccct	gcataccagc	agttacctgg	actcaccagc	11640
ttctgagact	ttggggaatt	ccatagcgta	aattgagttg	gttttctgct	ttttcccttg	11700
tcagttagg	atttagttct	tgtcgatctc	ccaaggcaat	agtccatttt	atctctagtt	11760
tcaaaaaaat	tattgctctt	cttctcttat	tctttccatc	cttggtggtt	tatgtcttgt	11820
gtaaaaaatt	ttgcttttaa	aaattttttt	cctgtgtgtg	agtgaagaga	gaagagagta	11880
gaaatagata	gatacattta	attcactatc	cttactcaga	agttgcatag	tttaaaattt	11940
tagaagtaac	taccttttcg	ttgtgccatc	ctcatttagg	cctttatcac	cttggttttt	12000
ttattaatct	tgtcttctta	cttctattac	ttcaaaactt	aaatctgtca	gattaatttt	12060
aatttatatt	ttcatcttgt	tactcagact	taaagttata	tgtttgtctt	tgttgaatct	12120
gatccaggtg	tttcatcgtg	gcattcaaag	ctttctcttg	gttagcactt	gacatcttac	12180
cttttatagg	tctttttctt	tctttttttt	tttttttttg	atttaaagaa	aaccattttg	12240
ttttcttcag	gggcaatttt	ttttttacat	tcaccacat	attatttata	tgtttatcat	12300
atttctttta	tttatttatt	tatttattta	tttatttttt	attatacttt	aagtttttag	12360
gtacatgtgc	acattgtgca	ggtagttac	atatgtatac	atgtgccatg	ctggtgcgct	12420
gcaccacta	actggtcac	tagcattagg	tatatctccc	aatgctatcc	ctccccctc	12480
ccccacccc	accacagtcc	ccagagtgtg	atattccctt	tcctgtgtcc	atgtgatctc	12540
attgttcagt	ttccacctat	gagtgagaat	atgcggtgtt	tggttttttg	atcttgcgat	12600
agtttactga	gaatgatgat	ttccaatttc	gtccatgtcc	ctacaaagga	catgaactca	12660
tcatttttta	tggctgcata	gtattccatg	gtgtatatgt	gccacatttt	cttaatccag	12720
tctatcattg	ttggacattt	gggttggttc	caataggtct	ttttctttac	agctcttcac	12780
agttgctgtt	atgtgtcacc	taatgacact	ttggtcatca	aaggactgca	tgtatgatgg	12840
tgggtccata	agattataat	ggagatgaaa	aattcctatt	gcccagtgac	atcatagttg	12900
tcataaggtc	ttagcacaa	acattacttt	ttctatgttt	agatacataa	atagttacca	12960
ctgagttata	gttgccatca	gtattcagta	tagtaacatg	ttgtacaggt	tgggagtaat	13020
aggctgttac	tgggagtaat	aggctacata	taggtatgta	ggctatacac	ctacatacct	13080
agggtgtgag	tggctgtacc	atctagattt	gtgtaagtat	actcaatgat	atcacacaa	13140
tgttgaaatc	tcctaagtag	acattttctc	gaacatatcc	ctgttggtta	gtgatacata	13200

-continued

actgtat	ttt	catatctccc	tttagacttg	ctcatgtact	tttatctatg	tggaatgcct	13260
ttttcttctt	ctttactttt	tttttttgag	acggagtttt	gctcttggtg	cccaggtctg		13320
agttcagtg	ctcgattggc	tcaactgcaac	ctctgcctcc	tgggttcaag	caattctcct		13380
atctcagcct	cctgagtagc	tgggattaca	ggcgctgggt	aattttttat	attttttagta		13440
gagacgggg	ttcaccatgt	tggtcaggct	ggctctgaac	tcctgacctt	aggtgatcca		13500
cccacctcgg	cctcccaaag	tgttgggatt	acaggcgtga	gccactgtgc	ctggctcct		13560
ttactttttt	taaggcccag	tttgatttac	ctttttgaaa	cttccccatg	ggctgggtgc		13620
ctgccttctt	tatttctttt	agtctctct	tcataattgag	catcttctct	gcaagtacta		13680
tggcaggcct	taatttaaac	caggattatc	ttctctgaat	ttacctggca	ctcttttttt		13740
tttttttgag	acagagtctc	attctgttgc	ccaggctgga	gtgcagtggc	atgatctcgg		13800
ctcactgcag	cctttgcctc	ccaggcgatt	ctcatgcctc	agtctcccaa	gtagctggga		13860
ttatagacgt	gtaccaccac	acctgactaa	tttttgatt	tttagtagag	acgggatttt		13920
gccgtgttg	tcaggctgggt	ctcaaaactg	accttaagt	atctaccac	ctcagcctcc		13980
taaagtgc	gggttacagg	catcagccac	cgtgcctggc	ctccatggta	atcttttttt		14040
ttttttttt	ttgagacgga	atcttgcct	gtcaccacag	ctagagtgc	gtggcacgat		14100
cttggtcct	tgcacctcc	gccttttggt	ttcaagcgat	tcttctgcct	cagcctcccg		14160
agtagctggg	actacagggt	tgcgccacca	tgctgggta	atttttgtat	ttttagtaga		14220
cacggagttt	caccatattg	gccaggctgg	tctcgaaac	ctgatgtcgt	gatctgcctg		14280
cctcgccctc	tcaaagtgc	aggattacag	gtttgactcc	atggctactct	tatatcctat		14340
ataaacgtat	tactaaaagt	atgaactttt	ttttttttt	ttttttttt	acagaggcag		14400
gatctcacta	tgttgctcag	gctagttttg	aactcctgag	ctcaagcaat	cctcatgcct		14460
tgacctccca	aagtgcctgg	attataggca	tgagccactg	cacttgcccc	tgaacttttt		14520
tttttaattg	aaaaagtgtt	ttttcttagg	aaagtaacat	atgcttacta	tttcaaat		14580
ataggctgaa	atagaaaaat	tagcagtaac	ataaaaatat	actcagcctt	aatgtatggt		14640
aaactaacag	tggtaatgtt	tttttaccaa	gaaaatgacc	acaaatttga	aggattccca		14700
aaacacagt	ctgttgagg	tatggctaaa	ttgatgcagt	ggatgaggct	ttaaattggt		14760
ataacctcct	tggcaggtaa	tgggcaatca	gagtttttaa	tgtgtctacc	cttaggceca		14820
gggagtcatt	ttcagaaata	atatggaagt	actggcacct	gtgcatgaag	atacacaatg		14880
atgttccttg	aaacattatt	tataatagtg	aaggtttgaa	tgtcataact	atacatttat		14940
agtacagagt	actatgtaac	tgtaaaaaag	aatgatctac	gtgtgtat	attgccatag		15000
caatatattg	ttacgtggaa	gggaaaaagt	tcagaataag	tacatctgta	cttatgggtg		15060
ggttatggct	tgataaaccc	attgtaaatt	gaaaacatcc	taagtcaaaa	atacatttaa		15120
tacacttaac	ctattcttag	cctagactac	cttaaatgtg	tgtggaatac	ttacatttagc		15180
ctgcagtggg	caaaataatc	taacttaaat	tctactttat	aataaagtac	tggatattat		15240
gtaatttaca	gaacactgta	cattacactg	aaattgtaat	ggtttccac	tatcataaag		15300
gtgaaaagcc	ctacatggaa	ccattataag	tcaggactgt	ttgtatagta	tgaccctttt		15360
ttttgggtaa	aaattaccga	aacctggct	ggcggtgggt	actcatgcct	gtaatcaggc		15420
acataccaca	tgtatggcca	attttgttca	tttttttttag	agatagggtc	tcactgtggt		15480

-continued

gcccagggtg	gtcttgaact	tctggactca	aatgatcttc	ctccctcggc	cttttaaagt	15540
gctagcctta	cagggtgaag	ccaccatggt	cagccccaca	gtttctttat	ccgttaacct	15600
gtagatagac	acttgggttg	ccctcacctt	tgactactgt	tgaatagtag	tctgtgaac	15660
gtgggtatac	aaatgtttct	ttgagaccct	gctttcaatt	ctttcaggta	tatacccaga	15720
ggtggaattg	ctggatcatg	tggaattctt	atttttaatt	taattttttt	tttgcgatgt	15780
tgtcttgctg	tgtttcccag	cctgatcttg	gactcaagat	tctcctgcct	cagaccccca	15840
gtagctggga	ctacagggtg	gcaccactgc	accaggtttt	atttttaatt	tttggaggca	15900
tctccatact	gttttctatt	gctgttacgc	cattttacat	ttccactagc	agtgcataag	15960
ggttttaatt	tctccacatc	cttgccaacc	ctttatttat	ttatataatt	ttggataata	16020
gtcatcttaa	tgagtagcaa	atgctttctc	attgtgggtt	tgatttgcat	ttccctagcg	16080
attgggtatg	ttgagcactt	tacatgtatt	tattggccat	tagtatatct	tctttgtaga	16140
aatgcttggt	caagtctctt	gcccatttta	aaattgggtt	tgctttttgt	tgagttgtag	16200
gagctcttta	tatatattgt	tttatttttt	atttgtttat	ttttttgagg	cagagtcttt	16260
ctctgtcgct	caggctggag	tgcatgtgtg	cgatcttggt	tactgcaggt	ctccgcctcc	16320
tgggttcaat	taattctccc	tgccctcagc	tcccagtagt	ctgggattac	aggtgcccac	16380
caccattcct	ggctaattgt	tgtattttta	gtagagatgg	gatttcacca	tgttgatcag	16440
gctggtctcg	aactgctgac	ctcagggtgat	atgcccgcct	tgccctccca	aagtgctggg	16500
attacagggtg	tgagccaccg	tgccctggcca	ctctttatat	attttggata	ttctgtgttg	16560
catatatgat	tcgaaaaatt	ttttttctgc	tgggcacggt	ggctcatgcc	tgtaatccta	16620
gcattttggg	aggctgaggt	gggcgatca	cttgaggtca	ggagttaaag	accagcctgg	16680
ccaacatggt	gaaaccccat	ctctaataaa	aatacaaaaa	ttagccaggc	gtgggtggtgc	16740
gtgctgtaa	tcccagctat	ttgggaggct	gaggctcgag	aatcacttga	acccgagagt	16800
tggaggttgc	agggagccaa	gattgcgcca	ctgcactcca	gcctgggcca	cagagtgaga	16860
ctctaactca	aaaaaaaaaa	aaaagaattt	ttttttttct	attccatggg	ttgccttttc	16920
actctgttgg	tagtgttatt	tgatgcacaa	aatattgtac	actatacagt	atgaactaac	16980
aaaaaacaat	gagatgtgtg	tagatagata	ttcatgatgt	atattgaaat	gacgagcaag	17040
ttgaagatca	ggcctccatt	ttttactaag	agaaaaatgc	accctttttt	tttttttaga	17100
caggatcttg	ctctgttgcc	cagggtggag	tgcatgtgtg	caatcacgac	tactgcagc	17160
ctcgacttcc	caggctcaag	tgatcctccc	acatcaacct	cttgagtagc	tgggactaca	17220
ggcatgggcc	accatgctgg	ctaacttgta	ttttttgtac	agatgagggt	tactgtgtgt	17280
gcaaaggcta	gtctcgaaat	cctgggctca	agtgatctgc	ccaccttggt	ctcccaaagc	17340
tctaggattc	caggcatccg	ccactgtgcc	cagcctgcac	ctctttttga	ttacagagtt	17400
aggtatatat	aaactgagat	tgaaaaataa	gagaaaaatat	actcagggct	gggctcagtg	17460
gctcaaacct	gtaattccag	tgctctggga	agctgagggtg	ggagtattgc	ttgagctcag	17520
gagtttgaga	ccagcctggg	gaacacagtg	agaccctatc	tctacaaaga	aaaaaaaaaga	17580
aaaaaaaaat	caccgagggtg	tgggtgtacc	catctgtagt	cccagctact	taggaagctg	17640
agacaggagg	atcactggag	cccgggagggt	tgaggctgca	gtaagccatg	atcatgccac	17700
tgtactccag	cctgggctgg	acaaagttag	accctgtctt	aaaaaaaaaa	aaaaaaaaagt	17760

-continued

actcagctgt tactaatggt tactgctggg ggatgagatt gaattggaag gagagaggag	17820
aggtacgggg ggcaggaaag ggagacaata atgagggact ttcagtttta ctttacataa	17880
ttttctttta agtattggaa tttaggtgat ttttcctttg gggttttctg tattttccaa	17940
tcacaataaa taaaataagt tataaatatt tgttgcata gaataatga taaacccatt	18000
tatgtatgta tttttttaa attagtatat tattaagtct atacaatatt agtatattgt	18060
tatgtatgta taagcttttt aacatgaagt ttgcagaata tagtacttct tccaaactct	18120
atgacatggg gggaactgaa gtatggggat atcttgtacc agtgaagaa ttcaagaaga	18180
gaccgtgtgt ggtggctcat gcctataatc ccagcacttt gggatgccaa agcaggatga	18240
tctcttggag ctaggcgctc aagaccagcc tgggcaacat atcaagaccc catctctaaa	18300
aaaaaaaaa aaaattaact ggggtgtgga gtgcgggcct atagtcttag ctattccaga	18360
agctgagggt ggaggattgc ttgagccag gagtttgagg ctgtagtac ctataccagt	18420
gattatacca gtgcactcta gcccaggcaa cagagtgaga cctggctca aaaaaaaaa	18480
aaaaaatcaa gaagagcaat ctggatatga gcatttggga ttttagcaa actgctgaga	18540
tttgtctat agcttgaacc tttcttttag ctaacttgat gatactgatg ataagcaagg	18600
actgtctttt taaaaatgt tacttcatta ttttcctgac agaaatgaca tcagatgtac	18660
catcactggg tccagccatt gcctctggaa actctggacc tggaaatcaa ggtggaggag	18720
ccattgtcca gagggctatt aagcggcgac cagggtgagt ttgagtgtag tgtgttatga	18780
atatctctcc tataaaccaa ctttagttgc tgaatttatt tagttgtga actcacttcg	18840
ctattctga ccatctcact tcaacttgat tacttactac actactgtca tataagtctc	18900
cttagtccct gtatttttgt ttatgaagaa tttgttttta tccaagtctc ccgtaagcag	18960
ttctttttt aaaccaaatt ttccgtaaga taaaggactg tagctaagcc cagagatttt	19020
actatgcctg agaaaactgt ttgctgcttt cattaagctt tgtttctgtt tccccaaat	19080
cattttggta ggctgctttt ctgaatttag agaattgctga gctctagaat agctgtcttc	19140
taagttattg atatgttgc tggtttggaa tgcagagtcc attcagctcc aaaagtattt	19200
attaaattcc taattagtgt tatggcattg tgcgtattcc aagtaggata caaagatgaa	19260
taagacacag tccttgttcc taagttggtt gtgttctgat agaaataatt attatacaca	19320
tgaatatatg atagaatatg cctagttttg tttaggaacaa atttgatact atgtttttct	19380
gtgtatggaa atatgcattt gttggtaaa actgagaaaa gcttcagaaa ggagggtgcc	19440
ttagaggggc ctggaagaat gggcactatt ttatttactt tttggtatta aattttcctt	19500
tttcttctt tttcttttta aaaattgtgc agctaattat aaccagtctt taagttttgt	19560
cccaccaata gtaatggaag agtgatgctt gggttcagtg gtaacatgag taacatatta	19620
agacttgta tatgttcagt agctttacag attttaacca tttgctgaag cataagctga	19680
ataagtaact ttctaagatt gtaaagctag taagtgtcag atataggata tgaaccttag	19740
gggttttagct ttgtagctta ctctttaaac actgtgttat gtttatgtac agtaacaaac	19800
aaaagtatta taaatatcaa aattagggca tcacttgaga aagtcatagt atatttaaaa	19860
tggaatgcta tgtagttata agcgacaaat atgtttcagt gtagaaagat gttcacaatc	19920
tattaagaaa ggttacagta ttatagtatt tcactgtcaa aagatatgta taacatgtac	19980
ataggaaaa actgaaagaa tatataccac atttctgggt aatagtatta tgggtgactt	20040

-continued

acgggtttctt	ttgtttttga	tttttcagat	ttttgaaatg	aacatgtatg	attggtaatc	20100
agaaaaatat	attaaaggaa	gtctttaaaa	attttctttt	tggttttttt	agagacaggg	20160
tcttgtagcc	tggtctggagt	gcagaggcac	aatcatggcc	cactgcagcc	tcaaaactcct	20220
gctcaagcag	tcctcctgcc	ttggcctccc	aaagtactgg	gattacaggc	gtgagccact	20280
tcacctgtcc	taaaagaagt	cttttaatat	ttcttttatt	tttatttact	tatttatttt	20340
cgaggcagag	tcttgctctt	ttgccaggct	ggagtgcagt	ggtgtgatct	tggtcactg	20400
caatctccac	ctctctggtt	caagggatcc	tcctgcctca	gcctcccaag	cagctgggac	20460
tacaggcgtg	cgccaccacg	cccagctaata	ttttgtattt	ttagtagaga	tgggatttca	20520
ccacgttggc	caggctgggc	tcgaactcct	gacctcaggt	gatatgccca	ccttggcctc	20580
ccaaagtgtc	gggattacag	gcagtagcca	ccatgcccgg	cctaataattt	cttttattta	20640
tttttttat	tttttatttt	tttgagatgg	agtctcgtc	tgctgcccag	gctggagtgc	20700
agtagtgtga	tctcagctca	ctgtaacctc	cacctcccag	gttcacgccca	ttctcctgtc	20760
tcagcctccc	gagtagctgg	gactacaggc	gcccgcctatg	atgcccgact	aatttttttg	20820
tattttcagt	agagacgggg	tttcaccgtg	ttagccagga	tggtctcgat	ctcctgacct	20880
cgtgatccac	ccgccttggc	ctcccgaagt	gcgggattac	aggcacgagc	cactgcaccc	20940
ggcccatatt	tcttttaaa	aaagattgga	aaatacagaa	agttagaaa	aacaataaaa	21000
aggccaaaat	ctactaccat	gttttttagt	gcattgtcct	cagtccttat	atgtaaatg	21060
tttttaatat	ttatgtaatt	atatagtttt	acatggccta	gtcttttcac	cttatataaa	21120
taataagcaa	tacacacgca	cacacacatt	ttggcacctt	atataataa	taagcaatac	21180
acacacacac	acatttcgga	gacagagtct	tgctctgttg	cccaggctgg	agtgcagtgg	21240
catgatcatg	gctcattgta	gcctcaactt	cttgggccca	ggaagcaatc	ctcctacttc	21300
agttctccga	gtagctggga	ccacaggcac	atggcaccat	acctggctat	tttttttttt	21360
ttttttaaa	acatggtctc	actacgttga	ccaggctggt	ctaaaactcc	taggctcaag	21420
cagccctccc	atctcgacgt	cctaaagtgt	tgggattaca	gacatgacct	actgtacctg	21480
gccctttaaa	aaaatattgt	tacatattct	atataaacat	aatttttatt	tatttttttt	21540
tgagacggag	tctcgctttg	ttgtccaggc	tggagtgcgg	tgatgcgac	ttggctcact	21600
gcaagctccg	cctcctgggt	tcattgctatt	ctcctgctc	agcctccga	gtagctggga	21660
ctacaggcgt	ccaccaccac	gtctggctaa	tttttttttt	ttttgtattt	ttagtagaga	21720
cggggtttta	ccatattagc	caggatgggc	tcattctcct	gacttcgtga	tccgcctgcc	21780
ttggcttctc	aaagtgtctg	gattacaggc	atgagccact	gcgcacagcc	ataaacataa	21840
tttttaattg	ttgcgtgaaa	ggatgtactt	aacttcctat	tttgggacat	ctaaattggt	21900
ttgaagattt	tgtgtgtaca	tatgatgcta	aaaagaactt	ctttgtacct	aaactttttt	21960
ttcctatttc	atattatttc	tttagattct	tagaaataga	gttattgggc	tgagcacgga	22020
ggctcatacc	tgtagtgcga	gcactttggg	aggctgaggt	aggaggatta	cttgagccca	22080
ggaattcaag	accagcctgg	ggaaaatggc	gagacttttt	tttctttgac	ttagcaatta	22140
tctttctttt	ccttccttcc	ttcatttttt	tcctttgact	tagcaattac	ctttccctcc	22200
ctcctccctc	ctctttcccc	ttcccttttt	tttttttttt	tttttgagat	gtagtctcgc	22260
tcttggtgcc	taggctggag	tgcagtggcg	caattttggc	tcactgcaac	ctctgcctcc	22320

-continued

cggttcagg	caattctcat	gcctcagcct	cccagagtagc	tgggattaca	ggtgccccgc	22380
accacacca	gctaattttt	gtatttttag	tagagacgag	gtttcacca	gttgactggg	22440
ctggtcttga	actcctgacc	tcaagtgate	cgctgcctc	agcttccca	agtgcctggga	22500
ttgcagatgt	gagccacagt	ggctggcccc	ttttctttt	tgagacagg	tcttgccatg	22560
tcactgaggt	tggagtgcag	tggcccaatc	tcagctcact	gcagcctga	cctcccaggc	22620
tcaaggcctg	cagccccctc	cgcccccca	accaagtag	ctaggactac	acatgcgcca	22680
ccatgcctgg	ttagtttttg	tatgttttgt	agagacggga	tttcaccgtg	ttgccaggc	22740
tggctctaaa	ctcctgagtt	caagtagtct	gctcgcttg	gcctccaaa	gtgcgtggac	22800
tacaggtgtg	agcaaccatg	cctggctgag	attttttaa	ataaaaaat	ttagttgagt	22860
gcagtgggtg	gctcctatag	ttccagctaa	ttgggaggcc	aagatgggag	gatcccttga	22920
gcccaggagc	tcaaggtggc	agtgagctat	gatcatgcca	ctgtactcca	gcctgagtaa	22980
cagagtgaga	gcttgctctc	taaaaagaaa	gaaaggaaga	gatagagaga	aagaaagaat	23040
ttgagttact	gggtagatag	ataggatttt	acaggtgacc	agattagggg	attcaggaag	23100
gaggaagagg	agcaaacact	ttcaggattg	atgctgtatg	tgtacttcaa	atgcgacca	23160
tctagaggcc	cataatatca	aggtatccca	atagtagaag	taaaaagagt	gatcactagg	23220
ttaaggtggt	aacatgagca	atatttttag	tcaatagtgt	acagagatta	taaggggatt	23280
ggtctatttt	attgtttata	atctttccta	atctccttta	aagaaattca	cttctctttt	23340
cctgaaatgt	ctgtagcatg	ttgattgtac	cccttatgtg	acactttcct	attctcactt	23400
gttttatatt	tgtatttctc	taggtgaaga	gccccttgag	ggcaagggtc	ttgtttttac	23460
ctcacctagc	acagtgtcct	gaatgaagta	tatattacat	gtttattaga	tcaatgaagg	23520
aaagaaacat	tatctaacaa	tcttcgtagg	tattaagtca	ctcctttatg	taagatcact	23580
gctttgaaag	atgtttcaga	aatttggtaa	cacggcttag	agcagactct	agaaatgaaa	23640
catggacctg	aattattttac	gttaattttt	tcttattttt	tctgagtggg	ttcctgctcc	23700
ctttacagag	gttgtagtct	gattgaaaac	tctggcaaag	attgactgct	actctaggaa	23760
agtgttaagg	tagcagaagg	tacttttggt	tctattgccc	agttttgtac	tttttttttt	23820
tgagatggag	tcttgacgtt	gtcgccacag	cttgagtgoa	atggtgcgat	cttggctcac	23880
tgaacctcc	acctcccggt	ttccagcaat	tctcctgcct	cagcctcctg	agtagctgag	23940
attacaggca	cccgccacca	tgcccagcta	atttttgtat	ttttagtaga	gatgggggtt	24000
cagcatgttg	gccaggctga	tctcgaactc	ctgacctcag	gtgatccacc	cacctcagcc	24060
ttccaaagtg	ctgggattac	aggcgtgagc	caccactcct	ggccccagtt	ttgtacttct	24120
ttgectagtt	tgggactatg	aacaagagga	aatgtagctt	tgtttgactt	ctgccacttc	24180
ctctttccat	tcttccattt	gggtgggtgt	tccggtagct	tgtgttgaga	aattttaact	24240
tcttaatggt	ttgtattatc	agcaggctta	aagtatttat	tgttggtttt	cctcaggctg	24300
gattttgatg	atgatggaga	agggaacagt	aaatttttga	ggtaagagac	tgaaaaactt	24360
tccttagatg	tctgatatta	aaaattagtt	tatgatcttt	atacttctga	cttgtaaatt	24420
ttgtcctta	ggtctaagga	gagtacttca	tcctaaaact	ataaatatc	atatatctca	24480
gaaaattttt	aagcattccg	ttaatatctc	tagagaaagg	acctcagtga	ggagaggacg	24540
gcatttacia	acctctctga	tcagttctct	gctacttcat	agcctaaaaa	gaacaacagt	24600

-continued

tcgttatcttc	tcaattctgt	ggattgactg	catgtttatt	ctgettattct	cacctagact	24660
cactcataag	actgcattct	cagctgggtc	gctgagaact	ggactcagct	gggatggctg	24720
gggtattctg	tctatgtgtt	tttttatcct	caaggaggcc	agactgaatt	ttttcatgtg	24780
gtgatggcta	caatctacag	cacaaatccc	agtgtgcaag	tgcttatcaa	gcctctgctt	24840
atatgacatt	tgcttatgtc	ccattggcca	aagcaagtca	tatgttccag	gtgtgagtgt	24900
gtgagggggt	tacacaagga	agtacatact	gagaggtgta	attcattggg	tgaggtgtca	24960
ttaatctgtg	actctgtcat	accctctgac	acctgttgac	acctcttata	ggtagcagga	25020
attggaattt	gtattttttg	tttttgtttt	tttttttttt	gagacggagt	cttgctctgt	25080
cgcaggaggt	gcagtggtgc	aatctcggct	cactgcaacc	tccgcctcct	gggttctagc	25140
gattctcctg	cctcagcctc	ccaagtagcc	gggactacag	gtgcgtgcca	ccatgcccag	25200
ctaatttttg	tatttttatt	tttttatttt	ttattaattt	tcttttttat	tgatcattct	25260
tgggtgtttc	tcgcagaggg	ggatttggca	gggtcatagg	acaatagtgg	aggggaaggtc	25320
agcagataaa	caagtgaaca	aaggtctctg	gttttcctag	gcagaggacc	ctgcggcctt	25380
ccacagtgtt	tgtgtccctg	ggtacttgag	attagggagt	ggtgatgact	cttaatgcgc	25440
atgctgcctt	caagcatctg	tttaacaaag	cacatcttgc	accgccctta	atccatttaa	25500
ccctgagtgg	acacagcaca	tgtttcagag	agcactgggt	tgggggtaag	gtcatagatc	25560
aacagcatcc	caaggcagaa	gaatttttct	tagtacagaa	caaaatagag	tctcctatgt	25620
ctacttcttt	ctacacagac	acagcaacaa	tctgatttct	ctatcttttc	cccacatttc	25680
ccccctttct	attcgacaaa	accgccatcg	tcatcatggc	ccgttctcaa	tgagctgttg	25740
ggtacacctc	ccagacgggg	tggcggccgg	gcagaggggc	tcctcacttc	ccagaagggg	25800
tggccgggca	gaggcgcccc	ccacctcccg	gacggggcgg	cggctgggcg	gaggcgcccc	25860
caccaccctc	ccgtagggg	cggctggccg	ggcgggggct	ggcccccgcc	tctctcctgg	25920
acgggggtgc	tggccaggcg	ggggctgccc	cccacctccc	ggacggggcg	gctgccgggc	25980
ggagatgctc	ctcacttccc	ggacggggcg	gctgcggggc	ggaggggctc	ctcacttctc	26040
agacggggcg	gctgccgggc	ggaggggctc	ctcacttctc	agacgggggtg	gctgccgggc	26100
agaggggctc	ctcaattctc	agacggggcg	gctgccgggc	ggaggggctc	ctcacctccc	26160
agacggggctc	gtggccgggc	agagggcctc	ctcacctccc	agacgggggtg	gcggggcaga	26220
ggcgtctccc	acatctcaga	ggatgggctg	cggggcagag	accctctcca	cttctctagac	26280
gggatggcgg	ccgggaagag	gcgctctcca	gttcccagac	tgggcagccg	ggcagagggg	26340
ctctcaccat	cccagacgat	gggcggccag	gcagagatgc	tcctcacttc	ccagacgggg	26400
tggcggccag	gcagagggctg	caatcctggc	actttgggaa	gccaaaggcag	gcggctggga	26460
ggtggagggt	gtagcgagcc	gagatcacgc	cactgcactc	cagcctgggc	aacattgagc	26520
actgagtga	cgagactcag	tctgcaatcc	cggcacctcg	ggagggccgag	gctggcggat	26580
cactcacggt	taggagctgg	agaccagccc	ggccaaccca	gcgaaacccc	gtctccacca	26640
aaaaaatacg	aaaaccagtc	aggcgtggcg	gcgcgcgact	gcaatcgag	gcactcggca	26700
ggctgaggca	ggagaatcag	gcagggaggt	tgcagtgagc	ggagatggca	gcagtacagt	26760
ccagcttcgg	ctcgccatca	gagggagacc	gtggaagag	agggagaggg	agaccgtggg	26820
gagagggaga	ccgtggggag	agggagatgg	agagggagag	ggctaatttt	tgtattttta	26880

-continued

gtagaaacag	ggtttcacca	tggtgggcag	gatgggtctcg	atctcttgac	ctcgtgatcc	26940
gccctcctcg	gcctcccaaa	gtgctgggat	tacaggtgtg	aggaatttgt	atttttgagt	27000
tgtaaatatt	ctggagcttt	taaaatggac	tatttatttg	tttgtttttt	tgagacagag	27060
tcttctctcg	tgcccaggc	tgagtgacg	tgctgcagtc	ttggctcact	acaactctcg	27120
ccttccaggt	tcaagcgatt	ctagtgcctc	agcctcctga	gtagctggga	ctaccacacc	27180
tggtcaat	ttgtattttt	agtagagacg	gggtttcacc	atgttagcca	gactggtctt	27240
gaactcttgg	ccttaagtgg	tccacctgcc	tcagcttccc	aaagggctgg	ggttataggg	27300
ataagccacc	atgtccagcc	tattttcttc	ttattttttt	gagacagggt	cttactctgt	27360
caccagact	ggagtgcagt	ggcacagtct	cggctcacta	cagcctcgaa	ctccagggct	27420
caagcgatcc	tcccacctca	gtctcccaag	tagctgggtc	tacaggtgtg	agccataata	27480
cctggcta	tttaaatga	tggtgccag	gctggcttta	aactcctgtg	ctcaagcaat	27540
cctcccacct	tggtcttcca	aagtgttggg	attacaggca	tgagccactg	taccggcct	27600
gaaaatggac	cttttaatat	attgatgaag	gagttcttcc	agaaaagggg	gatattcttg	27660
ctgaagacca	attgcttgtc	ttcttttcaa	gtaagaaaaa	cagtaagact	caaaagggaag	27720
agaactttga	ccgcaatctg	ctttttttct	ttccagagtt	gaaaatatta	cccaggtagt	27780
ctgtacgttg	ctgagtaaca	gacaatttga	taaaggagcc	caatgaaaaa	aaaatgattt	27840
gattgtgtgg	tgcccagat	ttaatatcat	ttatttat	tctttcttcc	tttttttttg	27900
agactgattt	tactcttgt	tgcccaggct	ggagtgcatt	ggtatgatct	cggctcaccg	27960
caacctctgc	ctcccagggt	caagcgatcc	tctgctcca	gcctcccgag	tagctgggat	28020
tacaggcatg	cactaccatg	cccggcta	tttgattttt	tagtagagat	ggggtttctc	28080
catgttggtc	aggctggtct	tgaactgccg	acctcagggtg	atccgccacc	ctcggcctcc	28140
caagtgtctg	ggattatagg	catgagccac	cacaccgggc	ccatttcttt	ttcttatttg	28200
tttgttttgt	taactaagtt	ttttctttaa	ttgggaaagt	aatataagtg	tattttatta	28260
cagaaatttc	aggctgggcc	tggtggctta	cacctgta	cccagcactt	taggaggctg	28320
agggtgggtg	atcgcttaag	ctctggaatt	caggaccagt	ctgggcaaca	tgccaaaact	28380
ccatctgtac	aaaaaatggt	acaaaaatta	gctggaaagt	ctggtgtgtg	cctgtagtct	28440
cagctactcg	ggaagctgag	gtgggagggt	ggtttgagtc	ctggaagcag	agattgcagt	28500
gagcggagg	tgccgactg	ctctccaacc	tgggcgacct	tgctcaaaa	aagaaaaaca	28560
acaaaatttc	aaacagtgca	gagttatata	tagtgaaagc	acatcttcgt	tttactttgg	28620
accttcagaa	ctcctttttt	tttttttgag	aggagtctcg	ctcttggtgc	ccacgttgga	28680
gtgcagtgg	tcgatctctg	ctcattgcgt	cctccgcctc	ctgagttcaa	gctattctcc	28740
tgctcagcc	tctgagtag	ctgggattac	aggcgccctg	caccatgccc	ggctaatttt	28800
tgacttttta	gtagcgacaa	ggtttcgcca	tggtggccag	gctggtctca	aactcctgat	28860
ccactcggct	cggcctccca	aagtgtggg	attacaagtg	tgggccactg	ccccagcct	28920
ggaccttcaa	aactctttag	acaaactacag	tttccagttt	gttgagtatc	cttccaaaaa	28980
tagtatatat	agaattgtat	ataaatgtgt	atgtgtgagc	atacacacac	ttatctcttc	29040
agtttttttt	acacaaagga	tgtccatatt	gtaaattgct	tgccattttt	tagttttata	29100
ttgcttcata	cagttaatat	catctatctt	ctttttttat	agtaacattt	aaagttaagg	29160

-continued

ctcatatttc	tggtactca	ctagatgaac	tttgccaaat	actottgaaa	acaacaaccg	29220
tgacttgccc	atcataaaga	aatagttgca	agtgggaagta	taattctcta	agaggctctct	29280
tgagacttaa	tgagtctcag	taaagtgtgaa	gaagggaaga	gatttcaatt	tctggagaag	29340
atagactttt	tcaaacagct	ttattgagaa	ttcctcctat	tgagaatcct	gaattataat	29400
gatacatgct	attagtggaa	cttcaactgtg	tgtatgaaag	atatgagggt	aaccactagt	29460
ctttttttat	acccgtgaat	tagctctaac	cctgagtcac	tgcttcata	aaatccagta	29520
gtcacaacta	catgcagatc	caaagagagg	ttcgttgtgc	cttttcctaa	ccataaaaaa	29580
agactatcgt	agtttatctt	accaagtcgg	gttgttgtgc	ctgagaaaag	cactgccgaa	29640
ttccctttcc	cccttctttt	ttttttttt	tttttttgag	acggagtcct	gctctgttgc	29700
cacaaatgca	gtggtgtgat	ctcagctcac	tgcaacctcc	gcctcccagg	ttcaagtggg	29760
tctgctgcct	cagcctccga	agtagctggg	actataagca	cgtgccacca	caccagctca	29820
atttttgtat	tttttagtaga	gacgggggtt	caccatgttg	gccagagtgg	tctggatctc	29880
ttgacttcgt	gatccgcccc	gtgttggcct	cccaaagtgc	tgggattaca	ggcgtgagcc	29940
actgcgcccc	gcctccccct	tctttttctg	ggtatatata	tacaaaataa	tcgaaggcag	30000
aatcttgaag	agatatattgc	acactcatgt	ttattggccc	attttgcgca	atagataaga	30060
ggcggaagta	accgaaatgt	ccactgacag	atgaatggtt	acagaaaatg	tagtatgtac	30120
atacaaggga	atattattca	gccttaaaaa	gaaagaacct	gtcatatgct	gcaagatgga	30180
tgaatcttaa	ggacattata	ctgaaagaat	aagccaataa	caaaaagaca	attactgtat	30240
gattccactt	acatgaggta	tctacaagta	gtcaaattca	tagacacaga	aagtaaaatg	30300
gtggttgcta	ggggttgggg	tgaaggagaa	atgagaaaat	ggtgtttgat	gagtatagag	30360
tttcagtttt	gcaagatgaa	aaagtcttag	atatctgttg	cacaacaatg	tgaatatggg	30420
tagcactact	caactgtaca	cttaaaaaatg	gtatacagta	aattttatgt	gttttttacc	30480
agaattaaaa	aaaaacccaa	aactaaccct	ttacttttaga	attgtgctga	caggccagtc	30540
agctgtgttg	tcattagatc	atcatctttt	tttgggtgtg	ctggtaaggg	taatggaaat	30600
accagaaacc	tgacaaataa	tagttgtggg	tcttttaagt	tctatggggg	gctgctgtta	30660
tttctatcac	tttgtgatgc	ttttccattg	gctttttttc	tattgaatat	ttcaccct	30720
ttctagttta	cttttcagag	tgaaatagat	ataacaagtg	taatgctttg	aaacaatcct	30780
ttttctctcc	ttcaggtgtg	atgatgatca	gatgtctaac	gataaggagc	ggtttgccag	30840
gtaaatattgt	agtaggtaat	atattgtaat	atataaatatg	atccatgttg	tagaaccaga	30900
cagtcctagc	atattgactt	aattttttct	ggatgagacg	gaatttctct	gtttaatata	30960
tttctatatt	ggaagtattg	gaaacttagt	attataacta	tcatttatgt	tcagggtgaca	31020
tggttcaaaa	ctggcgggat	attttatata	gtgtttttct	gtgtatgtga	taactaaagc	31080
aatgtgcttg	caaggtttcc	ataggagcac	aaattatgga	ttttgtgctt	gcatttatta	31140
ttaaatggat	ctacaaaaat	aggaatacac	ataatgggtc	tgaattaat	ttatttat	31200
tgagacagag	tcttgctctg	ttgcccaggc	tggagtgcaa	tgccgccatc	tcggctcact	31260
gcaaccttca	cctctgggtg	tcaagcgatt	ctcctgcctc	agcctcctga	gtagctggga	31320
ttataggccc	ctgccaccac	gccagctaa	tttttgatt	tttagtagag	atggggtttc	31380
accatgttgg	tcagggtgat	cttgaactcc	tgacctgtg	atccgccgcg	ctcggcctcc	31440

-continued

caaagtgcctg	ggattatagg	tgtgagccac	cgcacccggc	ctatatttatt	tttttgagac	31500
agagtctcac	tccatcaccc	atgctgtagt	acagtgggtg	aatctcggct	cactgtaacc	31560
tctgectcct	gggttcaagc	tgttcttcca	cctcagcctc	cctagtagct	gggaatatgg	31620
gcatttgcca	ccatgcctag	ctaatttttg	taataatttt	ttttagcaga	gatggggttt	31680
caccatgttg	gccaggcttg	tctcgaactc	ctcacctcaa	gcgattcacc	cacctcagcc	31740
tcccaaagtg	ctgggattac	aggtgtgagc	cattgtgcct	ggcctattat	tttattttta	31800
gatatgtata	tttttagag	acattgtttt	cattgtgttt	cccaggctgg	agtacagtgg	31860
catgatcata	gctcactgca	gcctcaaact	ctgggggttc	agtgatcctc	ctacctcagc	31920
ttcccaaata	ttgggattat	atgcatagcc	accatgcctg	gttggctctg	tttttttaaa	31980
aatgacagta	agaggcgggg	agtgtgggca	tatgcctgta	attccagcac	tttgggaggg	32040
agatgcaggt	ggatcacttg	aggtcaggag	ttcaaaacca	gcctggccaa	catggtgaaa	32100
ccccatctct	actaaaaata	taaaaattag	cggggcatca	tggtagggcac	tcataatccc	32160
agctactcta	gaggctgagg	catgagaatt	gcatagagccc	gggaggtgga	ggttgacagt	32220
agcagagatg	gcaccattgc	actccagcct	gggtgacagc	aagattttgt	gtcagaaaaa	32280
aaaaaaaaag	acagtaagga	aacagttttt	gtgacaagta	gagttttgat	tgaaaaaaac	32340
ttaaatttgt	ttaaatatcc	tatcaagatg	atgaaatata	ctttttttta	ttaaattctt	32400
aaatgtcagt	tttcttttta	gaaagttttt	attaaatatt	aggcaataaa	ttatttcttt	32460
tttgaataat	aagtttgtag	ctacctcaga	aagatgaata	attcgttatt	tcaaaatcca	32520
gtgattaact	gagcacttag	cacttagtat	ttgttcgttg	ctgatgctcc	tgtctcggg	32580
aacatacttt	aagaaccgtt	gatgtagaga	gattagaaat	atcaggggaa	gtagttaaaa	32640
actattctgg	agtgggtgaga	tgcaatctca	ggctttgaat	tagagggtat	tacataaaat	32700
gcattgtagg	gatattttct	tggtagcagt	tatagaattg	attaaaggga	tggactgtta	32760
gactgtaggg	aggtagatag	gaagctgttg	aaataataag	acagctataa	aatcatgagg	32820
gcctgggtta	cagtggcagt	ggtaacagga	aaggagtga	gttaagaggt	ttttgaagaa	32880
taatttgttt	atcgaaacta	attgaaataa	atatttgtta	agtctttagg	atgtgaacca	32940
tctctaaaa	gagaagttaa	tcatagatat	ttggaggata	gtttttcaag	cttcattgaa	33000
aagttaggcc	atcagttatt	attggcagta	tcttgatgaa	atttcaaaaa	gccatgaaaa	33060
categcatga	atgatttttg	ttttcatttg	tctgctttaa	tgtgcatata	tttcattcag	33120
aaatactgag	gtggattagg	gattgtggat	ctgtagtagt	agtagtagta	gaaataggaa	33180
ttttagatgc	ttaacttttt	tttaataaac	agaattcatt	catatgatgt	gttaaggtag	33240
tgccctcac	atatcctcct	tgggatatag	agggctctta	aagctgaaaa	cttcttgaaa	33300
aacttttggg	attatatgca	tagccaccat	gcctgggttag	tctgttctct	ttaaaaatga	33360
cagtaagagg	ccgggagtgg	tggcttatgc	ctgtaattcc	agcacttttg	gaggcagagg	33420
caaaagtgc	tcaacttttt	gaaaaaaaag	aagttttag	tttgtaaagg	aactatctag	33480
aagaaataac	ccaaggaatg	taaaactcta	aactgctgaa	tactactcag	ttctccttct	33540
cttgtcatca	gaatatatgc	gtaaattttt	acattcttct	tcattgttac	tgtgttat	33600
tctgcctatt	gaccatttta	taaaaacatt	cccatatatt	gataagggtta	ttgtatttgt	33660
catttttaat	agctaaaata	tcttttagct	tgtaaacctg	tcatacttag	acattttatt	33720

-continued

cagggcctct	ttatctatat	aaatatat	aaaatggaat	tgacacattc	ctgacacaat	33780	
ggcctgccaa	caccttgcta	tttctcagt	tgccacccat	cattacagta	tctcagtttt	33840	
ctagaaaaat	ttagtgatgg	ttctttgtat	ccttctccag	tgagagggga	attgttactt	33900	
ttgatccatt	cctgtgtggc	tatactgcag	agaaatggca	aaaggaccga	atcaaagtta	33960	
ataattat	taggaacaaa	tcaataatag	aagatatgcc	agaaacctac	ctcttagagt	34020	
tatttatata	atttctccag	tgaaatctgg	ttggttat	tgtcattgtg	tggcacgtgc	34080	
atgtgttgtt	tgtgtgagag	ggagagagat	tatat	ttgtc	atcacttggt	tgatagtatc	34140
atctttaatg	tactctgtct	ttaatttctt	cattatagaa	tagcacatgt	ggatatcatt	34200	
ttctttccag	attgggagca	gtgcataaaa	atgggtattcc	tgaattccct	tggttggttc	34260	
ttgttcagac	tctgtatata	tttggtcctt	acagagatcg	attggcaaaa	tgctttctgt	34320	
gtttagatca	tgttaattta	ctatatattg	gctttgcttt	tatgttgacc	tttatcttgt	34380	
aagttacttt	ttctttatcc	taacagatgg	ctttgtagag	ttacaggcaa	ggttcctgcc	34440	
tataattcca	tttccctcct	ctcttctctg	catctgttta	gttctatata	cttttctctc	34500	
ttctttctcc	ttttcttttt	ttttctcctt	ccatttctct	tcctccctc	cttctttttt	34560	
tccttctctc	cctccccctt	tccttctctc	ttttttat	taatttttag	ttagttcatt	34620	
aattctat	ttaggtcgga	tgatgagcag	agctctgcgg	ataaagagag	acttgccagg	34680	
taggagaaca	gtgtctttta	gcatagatga	gcagatgatg	ctgctttttc	tatccttttt	34740	
cttactcttt	cttttcttcc	cctttctctt	tgtatttttc	cttatctgtg	gcaagagagg	34800	
acaagatttt	ttagaagttt	gagtgtaaca	ggaactttgg	cttcccccat	cagaaagtgg	34860	
gtgagttgag	ggaactttgc	ttagggattt	aagaaattgc	tattagtttt	aagttttttt	34920	
ttctttttct	ctttatgtca	gtactaagtt	tcacagaaca	aaaagctctt	agaagggaatg	34980	
caaccgtgcc	agttgggtgt	ttaacaggga	aatactcttt	ttatcagaaa	accaataaat	35040	
atatctgtat	ttgtgattag	ttcccagtat	ttaggcctca	gcattttactc	cacacctcta	35100	
ggaaactcac	acctattttc	ctatgaagac	tcacagccta	gattattctc	acaacagAAC	35160	
tagtggtgtc	ttgggtgacc	aatctttctt	tgcggtagtt	ttctagaaaa	gttttagttt	35220	
ccttgatgtg	gctattttaa	agaccaggtt	tctgtactta	cgtgtcagaa	atctgtcaga	35280	
tactaggaag	atgagtgtct	tatgtttgag	aatagaattt	tatgtcttag	gcaaagtgtta	35340	
actaaatatg	ggcctatgtg	gtgagaccct	ttttgccatt	tagaaaggag	actctagaat	35400	
tctcttggga	gactgttgtt	tgtaatgtag	aatgctgca	gaagaaatat	gcatagactt	35460	
ttctgttttc	tagtatctgt	gatttggggg	tgacttagga	aatagatcat	tgatgccaat	35520	
acctattttt	actatatctc	cccttttttc	tactatttcc	tctttaatct	gggtcacaaa	35580	
ctcattttgc	tgccagttta	actcgagctt	cttactaacc	ctttcactgt	tcagaaaatg	35640	
gatttggcat	gatgtggtgg	agaaaacatt	gtattgggaa	gagagcagcc	tggggaaagt	35700	
cacttaccta	cttgacctcc	ctttgtctct	ctcagaaaaa	agagatttat	gttagatttt	35760	
taattttctt	actttctttt	ttttttggac	aaagaacttt	tgttcaagta	gaattcttaa	35820	
gtggtaacag	aaataaataa	aagagataaa	gcaggccggg	cgcagtggct	catgcttgta	35880	
accttagcac	tttgggaggc	cgaggcaggc	agatcacgag	gtcaagagat	ggagaatatc	35940	
ctggccaact	tggtgaaacc	gcgtctctac	taaaaataaa	aaaaaaaaaa	actgggcgtg	36000	

-continued

gtggtgtgcg cctgtagtcc cagctacctg ggaggctgag atagcagaat tgcttgaacc	36060
cagaaggcgg aggttgacgt gagccgagat cccgccactg tactccagcc tgggtgacag	36120
agcaagactc catctcaaaa aaaaaaaaaa aaaaaagaa gaagagagat aaggcaata	36180
tttgagtaga agcagaaatg cagcatgttg catgattatc tccttgaggc atccccatgg	36240
aggacactga gaaacttaat gggcttttaa aaattcctgt tggaaaactg ctggattatt	36300
cctgttaaca gtgatattct tctgtcttaa ttttgaggaa gtcagtgttg gagctgtggt	36360
ctatttacct ggggtgagatt caaattgtct tgtcagacct ttaatcatcc tcctctccat	36420
tccactctc cagttaactt cgtcccagac tggggaccca tatgggactt ttagtagatg	36480
gtgtatctta agtcttgtaa gaagtttagt gcaactggcag cacaccaga taaagaaggt	36540
aggactttgt gcattaatgg gccaaataaa acttcaaaat cttcaaatc tgccttttaa	36600
tgttgcaaat aagagagagg cttaccatat tttatagacc aaggaaatct gtactatcaa	36660
ttcttgatc agctatggag ccacatactt gagttggcaa aaattgggtcc ttttattttc	36720
tggcctttaa atagtgaat tagtaagcat gggagttaac caagctgagg ttatatgttc	36780
cataggaact taagttagta aaatcagcat ttaaaaatac tatctttttt tttctcttgt	36840
tttttgtttt ttgttttttt ttgaaatgga gtcttgctct gccaccagg ctgaagtga	36900
gtggtgtgat ctgagctcac tgcaacctcc acctccaga ttcaagtgat tctctgtct	36960
cagcctccca agtagctggg attacagatg catgccactg tgccctgcta atttttgat	37020
ttttagtaga gacagattt caccatgttg gccaggcggg tctcaaatc ctggcctcaa	37080
gtaatccacc tgctccatc tcccaaatg ctgggattac aggcattgag caccatgcct	37140
gacctgtcgt ttcttaaaac agcttttgtt ctgagggagt ggtaatttac aaaggatgtg	37200
aagttccag gaaatagggg gaagggaatt acattatctt cttgttctct gtctgcctta	37260
ttagttctgt ttcattgttg ctttgcatga gaaggttggc aaaccttatt ttaactgtg	37320
agacttaagc atcactaaat ctgaatacca cattcttcag cagcacactt ggtatccata	37380
tcactctccc tgctacaaa tgaccagatg tgaccacctg gatggggctt ctctttcttt	37440
ccatgcaggg aaaatcacag tgaaattgaa cggcgggcag ggaacaagat gacagcctac	37500
atcacagaac tgtcagatat ggtaccacac tgtagtgcct tggctcgaaa accagacaag	37560
ctaaccatct tacgcatggc agttttctac atgaagtctt tgcggggaac tggcaacaca	37620
tccactgatg gctcctataa gccgtcttct ctcactgatc aggtctctgg gacttatagt	37680
tctgagagag tctggaatct ggggtgaatct cttgaaagt ttcgtttttt ggacaagaat	37740
tcagcttttc aggaagaagt cagacaatgg gaaaacgaat ttcaatcctt ggctataaca	37800
ttaattagca ttgggacaat gagaagtaga gaagagtgtg gaaaactatt taataagcta	37860
ataagtatta atatttgaga acttgactca tgaatatagc atataggatg gaagaagaac	37920
agtggaatca cagaggaaat gactatgtcc atggaaccaa ttttctttct tgcctttagg	37980
gttagagaag atggaagaaa tctattttct atccctgaag cagcttctag ttttagtaat	38040
agaatgaatc tgtcccacct ttggtgatag aagaactgag agtctaattg ttgcttaggg	38100
atgtgctctg ttacatgtga tcactatgaa aaaaagaagg cgtaaacatt ttctgccttt	38160
caggaacttc atctgaatat aagtatgtga gtggcaggat atcacagaaa ataacaggaa	38220
aatgcataaa gagaggaatt gtatttttta attagtaatt ttatgtggga ctagatagac	38280

-continued

atactgaagg gatggctaaa gtgaatagaa tggctagact tgagttagga tggtaggga	38340
agacttctga gggtaaggaa gccatgttct gttttggta ttaaaataac atgatcattg	38400
cagaaaaatt tggaaaaatg aggaggtata aggaagaaaa aaatttactt cagtatcaat	38460
caagtattcc cttaatgcc acaatttaaat caaatgatta gaaagaagga gagaatatag	38520
tttgagaaaa tggaataaga attttccaaa taggatgggc tacttaaaac tacatacttt	38580
gtagctatat acattgaaat agttaatatg ttctaacagt acatgtgcaa gtattcaaca	38640
gactccagtt atgcaccttt tgtgggcaaa ccagggtgtg tgtgctgtga gaaatagaaa	38700
gaatggtagag acaaatgggt ttctgggtgga aacagacatg taaataaata aattaaacat	38760
agaactagtt ctataataga agtgctgtaa tgaatcctgt aaaatgcaga tatggaaaaat	38820
gagttgggga gtagtggtgt ggattttggg aagcacttga gcaaaaacct agaagtgtgg	38880
aataattggg ttatgcaaag aaagtcaagt ggttttagcat gtttttggtg gataatagga	38940
aggtaggctg ggatctaagt atggaatgtt taggtgttaa agaatttaga ttttaatttt	39000
tatgcagtgg ggagacataa aaaatgtatt agatctggtg gcattttaag gattgattga	39060
aagcaggcgg actacttaat tagttttggt aaaagatgac taggacagtg acaaagcatt	39120
ggaaagtaga atcgataaaa ctgaattatc actggaatgt gagagaatag ttagattttg	39180
aggcttctag cttaggagga tgctgttaag aatattggaa gagcacggca ggtttttttt	39240
tttaagaggg aaataatgat tcaggttttg ggatgttgat gttgagttgc tggtagaata	39300
tttataaata ttttacagat acttgaaatt caagtctgct gaaagctcag gaaaaaacgt	39360
tagtcatgtc tagggctata gacttggtta ttatttcgta gtggggaaga gtgaatatgg	39420
tttcccagga agaaagtatg gtattaataa agagggttga agatgaactt tggaaatgtc	39480
tacatttaag acttgaacaa aggaaaggaa gtctgaaaca gaagaggaag caaaaattgg	39540
agtacagtct catagaagaa ggtagggaaa aataaaattt aaaggataag atggacgaca	39600
ttgtcacatt ctgcagagag gttgaataaa gtgatgaaga cccaggaaaa gggacttgaa	39660
ttggtaatta ggaggacatt agtaacctca ttaaaaatat atgtatgctg ttcttgccag	39720
aacaaaaacc aaaccaaaca ggaaaacagt agtttagagt gagagtgaag tgggattgag	39780
aaataattga aaggtaagag gataaagcca gtgaatataa cattattctt agtataagct	39840
tgctgctgaa aaagagagat gaggtgggtc aaactgaggg aagatttatc tagaattgag	39900
aaaacttgat cttttttata ggcctgaagg gaaagagaga aagtgggaat atttgtcaag	39960
caagatccta aaaagagacc agagaggatg gaattaagaa gtcaattatt gttcatggta	40020
agcctttttt tttttgagac aggggtctct gctctgtcgc tcaggctgga gtgtgggtgt	40080
atgatctcgg ctactgcaa cctctgtctc ccaggctcag gtgatcctcc cacctcagcc	40140
tccggagtag ctgggactac aggcgtgtgc caccacacct ggctagtttt gtttttggtt	40200
ttgttttggt ttgttttggt tgtttgtaaa gatggagttt cgccccattg cctaggtgtg	40260
tcttgaactc ctggactcag tgaccctccc actttgacct cccaaagtgc tgggattacc	40320
ggcgggagcc gctgtgccta gcccaagcct ttttattctt cttgaatcct gagatagaga	40380
ggaagaggtg gatagtgaca tagagaaagt gaggaaacat gtattagaaa aaactttctt	40440
atcgatgaac tacatttagg gtggaaacct gtggctgtgg atcaggtgtg aaccagcagt	40500
tgcttacgga gagatgcatg tggcctgaag tgtcttactt cttcctgtga atagaaatac	40560

-continued

ttgttttttc	agagtaaaat	attaacttct	atttcttttt	cttgccgagg	aactgaaaca	40620
tttgatcttg	gaggcagcag	atggctttct	gtttattgtc	tcatgtgaga	caggcagggt	40680
gggtgatgtg	tctgactccg	tgactcctgt	tttgaaccag	ccacagctcg	aatggtttgg	40740
cagcacactc	tatgatcagg	tcaccccaga	tgatgtggat	aaacttcgtg	agcagctttc	40800
cacttcagaa	aatgccttga	caggtgagag	ttatgtgtat	gggaaatgaa	tgagaagtcc	40860
tttcttggtt	tttctctgag	acttaagaga	tgttttagct	gttaaattgg	tttggtgact	40920
ctggcaaggc	ttcaagaatt	ttctacttta	atgaatatag	tcagttcttt	ttatccatat	40980
gagattatct	actttgtggc	tcagccttag	aaaatatttc	attggtgata	atattttaca	41040
tttatcttaa	tattggtata	aatagaacag	taaaagccaa	acctacaata	cttttttttt	41100
tccgttctaa	aagaattatc	catgttttta	tctcatttgt	atggataatt	atctggtatt	41160
ttttctacct	cctggtgctt	ggctttgtgc	taggttcaat	gataacagct	ttttattcta	41220
tagatatggt	tattggtcaa	tgtataaggt	gttttctggt	gttggtgttg	ttgttgtttg	41280
tatctgtact	gttggtcttt	ttttctcccc	tattttatta	tgttcagtct	tttggccaga	41340
gtttggctag	aggaaacaag	tcatatctat	tcttgagcaa	ctctagaaaa	aaatttaaag	41400
tggaagcaga	taaaaaaact	ggtagttaaa	atgcaagaaa	tttcaatata	ctcatattag	41460
tgttggtgat	ctttagtttt	cctccttttt	tcccacccaa	aaaagagaca	gggtctctct	41520
cttgcctagg	ctggagtacg	gtggcacatc	atagcttact	gtaatcttga	actcttctgg	41580
gctcagtaat	ctgcctgctt	acagcttctt	gagtagctag	gagtagttca	tgtcaccaca	41640
cttgaccaat	ttttaaattt	ttttagagag	caggttctgt	ctgttgccca	gactggtctc	41700
aaactcctgg	ccttcagcat	tcctcctccc	atcttggtct	ctcaaagggc	tgggattatc	41760
ggcatgagcc	accacacttg	accagttttc	cctcctttta	tgtttttatg	atttcatttt	41820
tctagtctct	ccttttcccc	aaaagttggt	cttcgtttct	gtataataaa	gaagacaaac	41880
agatctatat	gtttctataa	catataaaat	tacttggttt	ttttcttttt	aaaatttttt	41940
ctttttatct	tttttttttt	ttttgagaca	aggtcttgct	ttattgctga	ggctagagta	42000
cagtgtactc	tcacaggcac	agtcatagca	cactacagcc	tcaaactcct	gccctcaagc	42060
agtcctcctg	cctcagcctc	ctgattagct	gggactacag	aaaagtactt	gtttttcaac	42120
caatgacatt	tactctgtat	gtatgtctgt	atgtgtatac	agataatcag	ctatgagaat	42180
atagccttgc	ctcttggttt	ctactactac	tttccactcc	tacttttctc	tgcacaatgt	42240
tattttcaat	gctgcctttg	aacttaagag	tgagattcat	tgatgataat	tgaagtattt	42300
taggcttgaa	aaaaaattca	tctcctgctt	ggtcagttct	gttataagca	aggagattaa	42360
gggcataaat	aggatgctta	cttatctttg	ccttcagtat	ctctccccct	cttccccaca	42420
cacaaaaatg	cactccagac	tgctcttcac	atcttccttc	agggcgtatc	ctggatctaa	42480
agactggaac	agtgaaaaag	gaaggtcagc	agtcctccat	gagaatgtgt	atgggctcaa	42540
ggagatcggt	tattttccga	atgaggtgag	tgtcaagctg	aggattgtga	tttggtatag	42600
gaaggatcaa	gagctgagag	ttttatttct	gtcagagtta	agttggatta	gctccagtgg	42660
attaaattta	actctccata	cccagatgga	ttgtaacaca	gaataaagta	tttggaagg	42720
gaactaacgt	ttctgaactt	gccagacact	atgatagggt	ctttatatct	gtcatcttat	42780
tttatcctca	caattgcctt	gtagtgtgag	attgatgggt	accattttgc	agatggaaaa	42840

-continued

acagatataa	agaaatgaac	ttggccaggt	gcagtggctc	aaggctgtaa	tcccagcact	42900
ttaggaggct	gaggcgagtg	gatcacctga	ggtcaggagt	ttgagaccag	cctggccaac	42960
atggtgaaac	cccatctcta	ctaaaaaaaa	acaacaacaa	aattagacgg	gcggtggtggc	43020
gtgcgccccat	aatcccagcc	acttgagggc	tgaggcagga	caattgcttg	aaccagagag	43080
gtggagggtg	cagtgaagccg	agattgtgcc	attacactcc	agcctaggca	aaaagagtga	43140
aactctgtct	caaaaaaaaa	aaaaagaaaa	agaaaaagaa	atgaatttcc	cactgttaca	43200
tactgtttga	tacaggattt	tgttttaatt	catagtagtc	tgactacaaa	acctctactt	43260
tttccctggt	acaacacaag	gcaatatcca	tttactcaga	ccatttcttc	tttttttttt	43320
tggttagaaa	tttgagactt	cctatgtctt	tcagtaggtg	tttagtgttt	ataaattata	43380
tactgtacgt	tttaggatc	tgtagaaaat	atggtgggtc	tttctataca	ggtacaaaag	43440
gcatctcagg	gtcacaaagt	tcaggctata	taatggaaat	tgactacatt	gtactgagag	43500
gatagttgct	agaaattatg	ggtaggatat	taaaggtttg	cttgagaggg	cacaaaattg	43560
aacattatgt	ggtttagtga	tttattttta	ttttatttta	tttatttttt	tgagacagag	43620
tcttgctctg	ttgccaggc	tggagtgcag	tggcatgac	ttgggtcatt	acaacctcta	43680
cctcctgggt	tcaagcgatt	ctcatgcctc	agtttcctga	gtagctggat	tgccaccaca	43740
gctggcta	ttttgtat	ttagtata	agtgtttcac	catgttggcc	aggetggcct	43800
caaactcttg	acctcaagt	attcgctgc	gtcagcctcc	caaagtgtg	agattacagg	43860
cctgaaccac	tgcaaccagc	gtgtaattta	gagtagcttc	tagaccaga	ctgctggatt	43920
ttgtttta	ccatattcta	tggatttgaa	ttctagcttt	gatgctatct	tctgaaacct	43980
tggatgatta	catgactaca	ttgtgctttg	atttcatcat	ctcacattgg	cgataatggt	44040
aatactgact	ttataaagt	gttatgaaga	ttagatgaat	taatatatgt	aaagatattt	44100
agaacagagc	atgacacata	ttaaccttat	gtaagtttta	ttttgtttt	aaaggatagg	44160
gagagggaaa	gtagcattgg	caggagtatc	ccaatatgtg	gacatggcta	atgcaaagac	44220
ataggcaaga	gcaagataat	aatgaactgt	agcaattaca	ttaagttgtg	gttaatgtag	44280
agcaggagta	agcaaacac	agccctttat	ttgtaataa	agttttattg	gaacatagcc	44340
atgccatat	ttttacatat	tatctatggc	tattttcatg	ctataatgct	agagttgact	44400
agttgcaaca	gactttctgg	cccgcaaagc	tgaaaatatg	tactatctgg	tcttttacag	44460
aaaaagcttg	ccaactcttg	atggtgagaa	tgtttgcata	tgaagaacat	atggaacatt	44520
ttgacttcaa	attctaaaag	ttttagaaat	actaaacttg	acctatcttt	atccttcatt	44580
attagtagca	ttaccaattt	tctatgtctg	gttgatcca	gagcatgtta	ttctgctatt	44640
actgtggaaa	gttctttgat	agggcagctc	gattgctttt	aatctcttta	ttccttgaaa	44700
cagggtgtggc	agtagctctg	tggaaccagt	ttctgtgaat	aggctgagct	ttgtgaggaa	44760
cagatgcagg	tgagatccta	agtggtgaaa	accaaaggga	tggccaaata	cctgcagaga	44820
tcatcacatt	tttacctgtc	ttactgtagt	cgttccttca	gcagctctca	cttgcacccc	44880
ttacctccca	cttaacatcc	cttacctccc	acttactttt	tttctggcaa	tattttccta	44940
aaacttctaaa	acttctcttg	aaaatcctgt	ttaagggaagt	cgctatgcta	ttttacctac	45000
tttctccta	ctgcatacct	tttggttact	ttactttggc	aagggtaaaa	atgtggcggt	45060
catttttggg	tgggaaagat	gattatcctg	ttttctaaac	tcctaagagc	ataaacttaa	45120

-continued

aagtactaag gcagcattgc cctttgagtt ttacgggtag attttttttt tttttttcaa	45180
actcctgtaa ctcttctagg aatggacttg gctctgtaaa ggatggggaa cctcacttcg	45240
tgggtggcca ctgcacaggc tacatcaagg cctggccccc agcaggtaag aaagtgaat	45300
agtaaatatt tccccttggc acagttgggt cctcacagag tccatgaaag ctaatattta	45360
ttatatacct ggatatgaa atgtactttt gtgtaagatg aaagaaaata ggaaaagaaa	45420
atgtacaatc cttcccttcc attattgagc ttttattcca gttgaggaga tagataactc	45480
aggctggaaa atgattcagt attggctgtg tcacagaatg tggtttttat gtgaacaaat	45540
ttatactgaa catatgtatt ctaagcattt gttgcaaaga aacttagaca ttgaatgcag	45600
ttaatttgag aaagatttct aaagtaggaa caagactttg agagaaaagg ggaaaatgcc	45660
ttttattgtaa taacttatca agaggatatt ctctgcaaag actttaaatc aagctttgag	45720
cagattagct ttaccagaac ttgaggtcaa acaagggaatg tgagaaagg gattgggttg	45780
caggatcaaa gttttaagtt ggcttgtcag agtttccaaa tcttagcaac tttattactt	45840
cctgctgcc tgggtattat tggaagtag gggttttggg gagacagaaa ctaagagaaa	45900
agagaagcaa ggtgatgtgt tttggaaaaa ggttaactt tggatgtgga gaaacctgga	45960
tgtgattcct gtcattgtta cttatttagt gcacaccta gggtaagtgt cttgaccttt	46020
ataaagctca gttttctcat ctgtaattca gagttagtac atcctgtata gggtttttgt	46080
gaggattaga tttaatgtaa ggaaagcatc cagcccagtg cctggcatat ggcaggtaac	46140
ccaataaaag taattaatgt aatttaaaaa aatttaactg aagtagtaat gacatttgaa	46200
ctacttagtc tatatactat ataagccaca cagttaaagt atgtgatctt tcatacctct	46260
atgtagcatc aaggaatact atttttctgg ataaaaagag tataactatg caaaaaacag	46320
gggagaaatg cagtcttctt ccttttctgt gtaaaacatt ggtttttctc ttttccaagg	46380
gacatgaata actattgatg gttggtataa cttcattttg ggttgcttgc taactttaaa	46440
agttacagat taggcaaagc ataaatttct tgcctataac atggtcatag aatggatgtc	46500
ttcatatgtg ccatatttgg ccagcatagt ttttttagagt actctgggta ggacttgat	46560
tttcagttt actataatta acatgggttaa aatgtaggaa ttaatatata tgtaaatact	46620
taaaacaatg actggcatat atggtaagtt ttatatactt gtttattctt atttatcatt	46680
ctctattgct ttatgcttag cctcttcata actagatgta ttttgttttg ttttgctttt	46740
tggttttttt tttgagaggg agtctcactc tgtctgtcgc ccaggctgga gtgcagtagt	46800
gcgatctcgg ctcaactgcat cctccgcctc ctgggttcaa gtgattctct cacctcagcc	46860
tcccaagtag ctgggattac aggtgcattc caccatgcct ggctaatttt tgtattttta	46920
gtagagatgg ggtttcactg tgtcggccag gctggctctc aagtgatccg ccaccttg	46980
cttcccaaag tgttgggatt acaggcgtca gccacggtgc ctggcccata aataggtcta	47040
ttttgaatct ttacttgtct gagttttgaa ggcatttgag ttggaggtcc ccgttaaac	47100
ttttaacgtc acgtttctga aggtgtttcc ctcccagatg atgaccaga ggctggccag	47160
ggaagcaagt tttgcctagt ggccattggc agattgcagg caagtatgaa ttttccacat	47220
ctatatcccc gttcaattag agcagatctt caggactcat tcctgttaat tttcttttac	47280
tttctgaata caaatgaaga attccataaa actctcaaaa tttgaaggaa tatggcattt	47340
atagtgacca ttgctattct tggatttaag taaagttgaa aagtatgaga ggaggagat	47400

-continued

ctttttcccc	ttgtcttaaat	tttagcttta	ctatgcttaa	ttttctatatt	ccagttaatt	47460
tcctttgccc	ctatacaaaa	gaagaaagat	ccttttcatt	gtatcattac	ctgactaaca	47520
atagaaaagt	ggaattatatt	tgattttttc	ataagtatag	ataagtttct	tggttacttg	47580
taccatatca	acctgagtaa	tgagttcagc	atagccagta	tgtggatttt	agattgaata	47640
aacttttatt	ttactttact	aacttggtaa	agtgtaaatg	tatgggagca	gagctagacc	47700
ttatgccttg	tctgattgtg	attgtcattt	ttttttcctt	tttggataaa	atgtgaaagt	47760
ttagaaagtc	ctaaaactgg	gaatcttatg	tctatgcaaa	agaccatgag	gagataggaa	47820
atacatctgt	aaataatggg	atcattttac	ctcattttta	tctcttcact	ctcaggtaac	47880
tagttctccc	aactgtacag	acatgagtaa	tgtttgtcaa	ccaacagagt	tcatctcccg	47940
acacaacatt	gagggatctc	tcacttttgt	ggatcaccgc	tgtgtggcta	ctgttggcta	48000
ccagccacag	gtgaggagct	ggagctccat	taggcctcca	ttttcctttg	gctatgttga	48060
cattatgtaa	tcatgtagtt	cctaagacag	ccaaaacata	tcaacctcag	ttaagaaaaa	48120
gagatcatca	tattctgtta	gtacctaa	ttattttcag	cttcctatta	ggactgtcat	48180
ctcatgtaga	gaaatatggc	ttgtcaaacc	aggtgggagc	agcaggtaca	aatatgtatt	48240
tattttttgt	tgttgatatt	aatacagatg	attcaaagg	actcatatta	attagttata	48300
ccagtatagc	tacatttaga	taattcatgt	aattacctaa	atgaataatg	gcccataaaa	48360
catgcagatt	tagcaccagt	tattataatt	tactcatgca	acagaccagt	tagccatctc	48420
tgaattgacg	catcatataa	acttttaaaa	ctgttggtgg	tcggaaggac	ttctggctgt	48480
ggctatgtga	aagaggttgg	tgaaaaagag	gtcttgaaaa	caaagaacaa	agagaattta	48540
cactacctga	ttcaacacta	actataaagc	tattaccaag	acactgtggg	gttgggtgaa	48600
ggatagatat	atagatcaat	agaccagaat	aaggtctatt	cttatacttg	tcaactaatt	48660
ttcagcaaa	gtgacaagac	aattcaatgg	ataaaataaa	tatttctaac	aatggaaca	48720
attggatatc	tgtatgcaaa	aaaaaaaaaa	aacaaaaaaaa	aaaccacacc	caaaaatgaa	48780
aacacataga	tcttacctca	tacaattttac	aaaaatcagc	ttagaggcct	aatgtgtaa	48840
gagctaaagt	tacaaataaa	ctcctaggag	aaaatctttg	tgattttgag	ttaggcaaaa	48900
gattttcttac	actaaaagca	tgattcacag	aagaaaaaaa	attataaatt	ggatttaatt	48960
gtaattaaaa	tttgccctct	ttaaaggata	ttattaagaa	aatgaaaaga	ccagacataa	49020
atggagagaa	aatagttaca	agtcataac	ctgaaagagg	attgtacca	ggaatatata	49080
aacaactcat	taagacaaac	agctggtaaa	aaagagcata	agacttgaca	tttgactgaa	49140
gaataaatat	gcattttatgc	acatgaaaag	atgctcaaca	tctttttacc	attaggaaag	49200
tgcaaattaa	aatcacaatg	agataccact	atataccac	tagaatggct	gtaatcaaaa	49260
agtattgggtg	aaaatgtgta	gaagctggaa	ggaaccctca	tacattgctg	atagacatgt	49320
aaaatgggtat	agctactagc	tttgcaaaag	catttttgca	gtttcctaca	aagttaaaaa	49380
tactcttagc	ctataaccta	gcaattttat	tcctgagtat	ctacctaaga	gaaatgaaaa	49440
catgttcacc	catagatttg	tacacagttc	atatctgtat	tattcataat	agccaaaaaa	49500
atgaaaaacta	tttaaacgtc	cattaacatt	ttgtaaatga	atacacaact	gtgttgatc	49560
catgtgagaa	tactactgag	cataaaaagg	aataaactac	tgataatgca	gccatgtaga	49620
tgaacttcaa	aaataccatg	ctcaatgaaa	gaagccagac	ccaaaagacc	acatattatg	49680

-continued

ttgttttatt	tatatgaaat	ttgtagaaat	agcagaacta	gagaggcaga	aagcagattt	49740
gtggttggt	ggggagtgg	agtgggagca	gagattgact	gcagatggca	caagggaaaca	49800
tcttggggca	gtgaatgtgt	tctgaaactg	gattgtggta	atcattgcac	aactataaat	49860
ttagtagaca	tcatcaaact	atacacttag	aatggctgaa	ttaatgaatgt	aaattttatc	49920
taaaatttat	aatctcatta	aaataaatgt	ataatattct	gagaaagaaa	aatgttttag	49980
aagccagctc	cttaacagat	tctgcctttt	tttagtagat	ttcatctttt	gtttattgtc	50040
tttttttttt	ctcctcctca	cttaactata	atcttaggat	taaaacagaa	gaaataaaat	50100
ccagggtccc	agctgatgga	ccaggccagt	tagatgacca	taaaattata	tatgttggt	50160
gggcacgggtg	gtcacacct	gtaatcccag	cgctttggga	ggccgaggcg	ggtggatcac	50220
ttgaggtcag	gagttcgaga	ccagcctgac	caacatggtg	aaaccctgtc	tctattttaa	50280
aaaatacaaa	attagccagg	tgtggtagca	caccctgtga	atcccagcta	cttgggaggt	50340
tgagacagga	aaattgcttg	aactcaggag	gtggaggttg	cagtgaacca	agatcgcgcc	50400
atcgtactcc	agcctgggca	acaagagcga	aactccatct	taaaaaaaaa	aaagtatata	50460
tcttactctt	ctttctgtat	tctaggaact	cttaggaaag	aatattgtag	aattctgtca	50520
tctgaagac	cagcagcttc	taagagacag	cttccaacag	gtaacttttt	tctggtttt	50580
gttctgaata	aatatttgtc	atattcactc	cataaatatt	gactactgat	taactgaaca	50640
ctgtggcagg	cactacagtt	ttatgttctt	tagtagttaa	tctgcatttt	taaggaatag	50700
aaaaggacta	atactttgaa	attatggata	atgcccagg	tatttctgtt	tggctttggc	50760
tatttactgt	cttgtattca	attaactgta	tccaaggagc	tgtctttaag	gtatttaaac	50820
tattgcgcca	ggcatggtgg	ctcatgcgcc	caacctctgt	agatgctgtg	aaaatagatg	50880
ttttcctcgt	ctgggcatgg	tggctcacgc	ctataatccc	agcactctgg	gaggctgagg	50940
cagggtggatc	acttgaggcc	aggagttcaa	gccagcctg	gccaacacag	tgaaccccca	51000
tgtctactaa	aaatacaaaa	aattagcctg	gtatggtggt	gcatgcctgt	aatcccaggt	51060
actcgggagg	ctgaggcagc	agaatcactt	gaacctggga	ggcagagggt	gctgtgaact	51120
gagatcatgc	cactgtactc	tagcctggat	gacagagcta	gactctgtct	caaaaaaaaa	51180
aagataaaaa	agaaaattgt	atacttact	aagctttag	tagaaaaatt	cattttatat	51240
agtttttttt	tttttttaga	aggagtctag	ctctgtcgcc	agggtggagt	gtagtgtgca	51300
atctcagctc	attgtaacct	ctgcctctta	ggttcaagcg	attctctgt	ttcagccccc	51360
cgagtagctg	ggattatagg	cacatgctgc	cacgccagc	taatttttgt	atttttagta	51420
gaggcggggt	ttcacaccgt	tggccaggat	ggtctcgatc	tcctgacctc	gtgatccacc	51480
cacctcagcc	tcccaagggt	ctaggattac	aggcatgagc	cattgcgccc	agcctagact	51540
gttcttttat	ggatgagtga	gagtcgtaat	gaattatata	agctgactgt	taattgtcat	51600
tctcaggctc	cagctcctga	aaatatctgg	tgaattttat	agacatggct	tttgataacg	51660
gtttttactt	tgtattagac	aagttaatta	acctctttaa	gtctcagtag	tgtcgttatt	51720
gatacaatga	atatattaat	agtacctaaa	ttcagacggg	tgttgggaag	attaaataag	51780
gtaatgaata	taaaacacat	caccagctat	ttgatacgta	gtattacaaa	ataagtgggt	51840
agcttcta	actgtttatt	tttatttttt	taatttttag	gaatatagag	taaaagatt	51900
attttctatt	ccatgagact	agtatctaaa	ataacctaaa	attggctggg	catggctcgt	51960

-continued

catgcctgta atcccagcac tttgggagggc tgaggcaggt gatcacttga agccaggagt	52020
ttgaaccagc ctggccaaca tcttgaaacc ctgtctctac taaaaatata aaaattagcc	52080
gggtatgggt gctcatgcct gtatgccag ctacttggga ggctgaggca tgagaattgc	52140
ttgaacccag gaggcagagg ttgcagtgc ccaagattgc cccactgcac tccagcctgg	52200
gcgatatagc aagactgtct aaaaaataaa taaaaataaa aataaaataa ctaaaattac	52260
ttttaaaaaa taaaagcaaa acaagactaa agccaactta attttattta tggaaacctc	52320
tgtagatgct gtgaaaacag atgctctcat ctgggtgcag tggtctcacac ctataatccc	52380
agcactttgg gaggccaagg caggcggatc atttgaggtc aggagtttga gaccagccta	52440
gccaacatgg tgaiaacccg tctctactaa aaatacaaaa attagctggg cgtgatgggtg	52500
cacgcctcta gtccccagct actcaggagg ctgaggcagg agaatacatt gaaccttgga	52560
ggcgagggtg cagtgcagca agattgcacc actgcactcc agcctggcga cagagcgaga	52620
ctccatctca aaaaaaaaaa aaaagaaaaa gaaaagaaaa cagatgttct cagggttcgg	52680
ggaaaaata ggattgaaga gcaatatata agctatatct tgtgtcctta aacttaccac	52740
atttctggta tagacttgta aagctaggtc agagtatctt taatggattt cccaaggga	52800
gtagggaac agtcttttcc ttcctggaaa taagttatta ttcctatttg actagaatag	52860
tattaggttg gtgcaaaaga aattgtgatt ttttgccatt tttttaaatg gcaaaaaatg	52920
caattacttt tgcaccaacc taataagaaa gcttgagtct ctggccgggc tcagtggctc	52980
acgctgtaa tcctagcact ttgggaggcc gaggcaggcg gatcccgagg tcgggaaatc	53040
gagaccatcc tggccaacat ggtgaaaccc cgtctatact aaaaaataca aaattagctg	53100
ggcgtgggtg cagctgccta taatctcagc tacttgggag gctgaggcag gagaatcgct	53160
tgaaccagg agtcggagggt tgtatgagc cgagattgag cactgcact ctagcctggt	53220
gacagagcga gactccgtct caaaaaaaaa aaagtctggg caggtgggt cactctgta	53280
atcccagcac tttgggagggc cgaggcgggc ggatcacaag gtcaggagat caagaccatc	53340
ctggctaaca tggtgaaacc ccgtctctac taaaaatata aaaaattagc tgggcgtggt	53400
ggcacgcgc ttagtccca gccactcggg aggtgaggc aagaaatcg cttgaacccg	53460
aggggtgggt gttgcagtga gcagagatcg tgccactgca ctccagcctg ggcgacagag	53520
ggagactccg tctcaaaaaa aaaaaaaaaa gcttaagtct ctgaaaggaa gcatgagaaa	53580
tatgcttcca tgtttaatca cttagttttt actctcattt tgttttaata ttgaaaaata	53640
ttggtgcctc aaggacaatg acaagagttt tagggttata gaaattgaa aatttttatt	53700
tatttttgta atgaaaattt tctatgagtt cactgatgg catgaaaact ttttcaggta	53760
gtgaaattaa aaggccaagt gctgtctgtc atgttccggt tccggtctaa gaaccaagaa	53820
tggctctgga tgagaaccag ctcccttact tccagaacc ctactcaga tgaaattgag	53880
tacatcatct gtaccaacac caatgtgaag tatgtattat acaggagtgt gaaaaaactg	53940
tttttctct gttctcaca cagaaaacac ttctgatgcc ctatgtgggg ggttaacaat	54000
caagcaacaa cacaaaaatt tagccgggag tgggtggcatg tgctgtagt cccagctact	54060
ctggaggctg agacaggaga atcacttgaa cctgagagggt ggagggtgca gtgagctggg	54120
atcatgccac tgcactccag cctgggctac agagcgagac tccatttcaa aaaaagaaaa	54180
agaaaaaaga aatcaagcaa tcagtagtgg acaccagctg ggtgtccttc cattcaattc	54240

-continued

agttcactat ctacttggag atagcatcag atcccccatt ttgtgtatgc agtaccacaa	54300
gactgctccc acttctgatg ccagttgcaa gcccaggtt gttttacctg tgcattctgac	54360
tgaccagctg tctcccata cccctactt gggttcagtc aatttgcttg aatggctcag	54420
ggaacattta cctatgttta ccagtttatt ataaaggata ttacaaagga tactttgtac	54480
atcagatgaa gagatagata gggcaaggta aggaggaagg agtgcagagc ttccagaccc	54540
tttctgggtg ggctaccctc cggggatctc catgtgttta cctatcaaga agctcctcaa	54600
accagtcctt tttgggtttt aatggaaatt tcattatgta gccatgagtg attaaatcat	54660
tgccatttgg taatcaactt aaccttaggt accggctccc ctccatgagg ttgaggggta	54720
gggctaaaag tcccagccct ctaattttac cttgatcttt ccagagatga gcccctatct	54780
tgaagctacc taggggttgc cagccctcag tcaactcatt agcagacaaa aagacactta	54840
tcacactgaa gattccaaag attttaattg gtaaaaatcc aggtccactt atacatggat	54900
ttttttcagt aaatatatta gaaaattctt ttgatatttg tgacaatttg aaaaacccaa	54960
aaataagcta catagcctgg atatatgaa aaaattagaa aaagttagcc atgtcataca	55020
tgaatgtatt aaatatatat aaattctagt ctattttatc atttactacc atacaacata	55080
tacaaatcta ttataaaaag taaaaatgct ggacaggtgc agtggctcac acctgtaatc	55140
ccatcacttt atcacttttg gataccaagt tgggatacca agttgagcag atcacttgag	55200
gtcaggagtt cgagaccagc ctggccaaca tggtgaaacc ctgtctctac tgaaaaaaaa	55260
aaaaaaaaaa aaaagaaaat acaaaaatta gctgggcatg gtggcacacg cctatagtcc	55320
cagctacttg ggaggttaag gtatgagaat cacttgaacc tgggaggtgg aggttgagct	55380
gagctgagat cgcaccactg cactccagcc tgggtgacag agggagactc catctcaaaa	55440
aaaaataaaa taaaaatgta tcacaacgta tacatacaca ccgtttgtac aatggcacca	55500
ttttagttg agagaaatgt aaacaaatgt aaagatgcag ttttaaatca taaccgcgta	55560
aagttaacta tagtatatac tgtactgttg taataatttg gtagccacct attgctcaat	55620
tgttgccagt ttgcttaaaa tgctgtgtga tgctaatacat ctcttcatga gcaattcact	55680
ccagtaaatt gcatattgca gtaaacagtg aaatctcatg gttcttgcac atttttctac	55740
gtgttgagtg caatactgaa accttgaata acatttgga acagtatgaa gtgccactag	55800
tgatgctgga agtcttccca agaagcaggg aaaagtcag acattataag aaaaagggtga	55860
attgcttgat atgtactata gaatgaagtc tgcagctgtg gttgcttgcc acttcatata	55920
gatgactcat cttgtaagtc atcttgtaag atgatataag cttatgataa cgataaatac	55980
agtacagtgc tgtaaatgca ttttctcttc cttatgattt tcttaataac attttctctt	56040
tagctttatt gtaagaatac agtacataat acgtacaaca taaaaaacgt gttcaactgc	56100
ttatgttatt ggtaaggctt ctggccaaca gtaggctatt agtagtaacg ttttgggaga	56160
gtcagaagtt tacagtcgaa ttttcgatgg cacaggggtc agtgccccta gcctccatgt	56220
tgagcaatca gttgtatttc ataatacac ataggcattt tccaatgttg ggatttctaa	56280
tgtaccaact cttcttagtc ttatcaagct atccctttct cctctacttt tctagtatta	56340
aacaccatta gtttgaagtt cttcattttc cagcttatag gatttgggat agttgatcag	56400
agtagagtaa ggtttttttg ttttgttttg ttttgttttg ttttttcaga cagggctctg	56460
ctctggcacc caggctggaa tgcagtggtg tgatcatggc tcaactgcagc ttgaacctcc	56520

-continued

caggctcaag	tgatccctccc	acctcagtc	cctgagtagc	tgggactaca	gacatctacc	56580
aagacgcctg	gctaattttt	gtattttttg	tagagatggg	atttttccat	gttgcagagt	56640
ctggtcttaa	actcctgggc	acaagcagtc	catcgctctc	ccaaagtgt	aggatcacag	56700
gcgtaagcca	ctgcacctgg	ccagagtaag	attttacaaa	caataattca	gagactaggt	56760
cctgagatgg	aagggtttag	tttcaattct	atgtatcaac	tctttctgga	aaggactatg	56820
ttttgtacac	cagttttattg	ctctagtctg	gcaggatttt	cctctggagc	aggggtaggc	56880
aagctctttc	tataagtggg	gctagatagt	aaatatttta	ggctttgtgg	gccatgtggt	56940
ctttattcca	cctactcaac	tctgctgtag	catgaaaaca	gtcatagaca	aatgaaagaa	57000
tggggctgtg	ttccagtaaa	tctttattta	gaaaaacagg	cagtgggcct	gatttgggtca	57060
gttttcttta	gagcatagct	acatcctcct	ctttcattag	ttactgttcc	tctcttttgc	57120
acttttctat	ttgagttttc	tttctcagtt	tcttttttaa	aaagttttat	gagatatatt	57180
tcacatacca	tatacctcac	tcatttaaag	tatacagtgt	tttttagtat	atcacatagt	57240
tatgtaactc	ttactgcagt	ctaatttcag	aataatttca	ttccccaaaa	agaaattcta	57300
gatcagttaa	cagtcatttc	ctgttctttc	ccccggctct	gaaattctgt	ataactatga	57360
atctgttgtc	tttataaatt	tgtctattct	agacttttcg	tataaatgga	atcatagact	57420
ttgtaattcc	tttgtaactg	gcctatttta	cttagtataa	tgtttacaga	ggttatctgt	57480
actgatacat	gttgtagcat	gtatcagtac	ttcattttct	tttattgcca	aataagattt	57540
cattgtatgg	atataccaca	tactgtctgt	atgttcgtta	atggacattt	ggttgtttct	57600
acttcttggt	tatcaaaaat	gcttccatat	gtaaaatagg	gataaggaac	tgaaaaaatg	57660
ctttcatgaa	tatttgttta	ctagttttta	tgtggatata	tgtttttatt	ctcttgaatt	57720
ccaccaggga	gtggaattgc	tggccacata	gtaactctgt	tttacctttt	gaggaactgc	57780
caaaactgtt	tccaaagctg	ccccatcatt	ttgcattccc	aggagctctg	atcctccac	57840
atccttggtta	acacttggtta	ttgccttttt	ttttttattg	tagccatcta	gtaggtatca	57900
attgtcaggt	taccaccttg	ccatttaatc	ttttctttct	gtagaattgg	ccttgaatcc	57960
acctcttgaa	gatcagatta	tgactactta	gcaaataatga	ataataccta	gtgacaagtt	58020
ttgtccaatt	cagtcttttag	aacttgtaaa	gtttaattct	ttgctaacta	acttagtata	58080
acagagtgga	ttgagttaga	aatttttatt	aacttaggac	tcaagtggat	ggatcatggc	58140
attgtagttc	tttatttttg	tctctttgca	tctttatatt	acacaacagc	cttcattttt	58200
gtgtttccat	tttgtttaaa	tttttaaaaa	tttaagttgt	ttgaaggact	cgagtttctg	58260
gaaataattg	ctttctccat	gtttatgtat	cattttccct	accatgatta	attttaatta	58320
gcttttaggg	atttgtttgt	ttgtttgttt	cattgagaca	gtgtctcact	ctgtcaccca	58380
ggctggagtg	cggtggcgct	atctcagctc	actgcaacct	ccgcctccca	ggctcaagca	58440
atcctcccat	ctgtctcctg	agtatctggg	actacaggag	cccgccacca	cgctgctaa	58500
tttttgattt	ttttgtagag	acggagcttc	accatgttgc	ccaggctggg	ctcaaactcc	58560
tgagctcaag	caatccaccc	tgccctcagc	tcccaaagtg	ccaggattac	aggtgtaagc	58620
caccgtgcct	ggccagtatt	ttatttttaa	ataaatattc	tttatagaaa	atgtggaaag	58680
tattgaaaaa	tacaaagaga	aggaataaaa	ttctcacact	ccagatagtc	ttgtgtgatg	58740
tacagtgat	gtactttcat	ttttttacct	atgcttttaa	aaaatacctt	atatgaatat	58800

-continued

atacacacat	tcacaataac	cagggttttga	atacctagaa	ggagtttagaa	cccaacaaga	58860
tgacccctgt	gtcatagaac	atgggtttctg	tttgetgaaa	ctgacaccct	agattaaacta	58920
taggatagga	ctttaatgaa	ggattttattg	attgttccac	ctacagatga	atctatagag	58980
ctttacatac	agaatcttat	tcttctcttt	ctctctctct	cccccttcc	tccctctcca	59040
ccccctctt	actgtctact	ctggtttct	aggaactcta	gccaagaacc	acggcctaca	59100
ctctccaaca	caatccagag	gccacaacta	ggccccacag	ctaatttacc	cctggagatg	59160
ggctcaggac	agctggcacc	caggtaaaaa	agggtgaaat	aatcatctgt	tgagcagtca	59220
cccagggggt	ggtcatttgc	aatcccatat	atTTTTtgtt	cggttgggta	atTTTTtttt	59280
TTTTTTTTt	agaaggagtt	ttgctctcat	tgtcaggct	ggatggaata	caatggcacg	59340
atctaggctc	actgtgacct	ctgtctctg	ggttcaagt	attcacctgc	ctcagcctcc	59400
caaatagctg	ggattacagg	tgcctgccac	cacccccggc	taattttttg	tatttttagt	59460
agagacgggg	ttttgccatg	ttggccaggc	tgggtgcgaa	ctcctgacct	cagggtatcc	59520
acctgcttcg	gcctcccaaa	gtgttgggat	tacaggcatg	agccaccatg	cccggcctgt	59580
ttaatttgtt	ttaaggttct	ttctccagat	tcttttttaa	aaaaaatTTT	ttttctatt	59640
tgtcttgtea	actggccttt	gacatatagg	cagcagcaac	agcaaacaga	attggacatg	59700
gtaccaggaa	gagatggact	ggccagctac	aatcattccc	aggtgagttg	tgtcctcttc	59760
gttgaagagg	gtagggagta	tttacttagg	aagtgttctc	cggtagtagt	tagaatgtac	59820
atatgttgta	tatgaatttt	agggttattg	aattgtcatg	ttaaatcttt	aatggttatt	59880
tttatcattg	tattccacag	gtggttcagc	ctgtgacaac	cacaggacca	gaacacagca	59940
agccccctga	gaagtccgat	ggtttatttg	cccaggatag	agatccaaga	ttttcagaaa	60000
tctatcacia	catcaatgcg	ggtatgttct	tttctcatta	tccttttaaa	ttctcattta	60060
gatcacttac	tgatgggcat	gccactgccc	agtcagtaat	cttccagtgt	ttttccactt	60120
aatcataata	ccacctgagt	aaataggaac	ttgctgaact	aatatactac	agccccctga	60180
ctggcccttc	cccaactcct	tttggtccac	agatcagagt	aaaggcatct	cctccagcac	60240
tgtccctgcc	acccaacagc	tattctccca	gggcaacaca	ttccctccta	ccccccggcc	60300
ggcagagaat	ttcagggtgag	ccccgtatat	atgtgctgct	ttacagggcc	ctgagggatt	60360
cagctgctga	atccaaattt	tattcttccc	ttgctttctc	tggttacttc	agaaaaagca	60420
gtgaagcttg	tagggcctag	cgtgaggcaa	acaagctgct	tttcttcctc	ctatttcttt	60480
gcacctgtcc	tattgccatg	ttctaggctc	catctctgtg	tgtcctggtc	agtgtgtgac	60540
tgtcagtcct	tcttgtcttt	tccaaattgt	tatcaaattt	tccttaacct	gcaggaagtc	60600
aaggggatct	agggatagca	ctagattgtc	ctttgatctc	tagcttctgt	gataaatcta	60660
tccttttaat	cttttacctc	atttattcac	tcctaggaat	agtggcctag	cccctcctgt	60720
aaccattgtc	cagccatcag	cttctgcagg	acagatgttg	gccagatTTT	cccgccactc	60780
caacccacc	caaggagcaa	ccccaaactg	gacccctact	acccgctcag	gcttttctgc	60840
ccaggtaaaa	cttatcatct	gtgtgttccc	tgtgtattat	TTTTtTTTg	tttgggcttt	60900
tttcggtatg	taaaatcagt	gttttctatt	ttaataacct	tctcccaaac	cctgttctc	60960
cggtttccaa	tttccatctt	tgttgagagt	agctaattaa	aatcacaga	taataaaaaa	61020
aaatctcagt	agagtctgtg	gttttcacct	taaatcagaa	ttgctcactt	ggaacgtttt	61080

-continued

gagcacgtct gattttcaga tttgttttgg agtaaattct aagatgtttc ctctttgttt	61140
aggactccat aaggcaggag caaaggagaa aattaatgac taacttacag tgatgtctgt	61200
ttacaaaaaa gttgaaaaat tctttttttt tttttttttg agacagagtc ttgctctgtc	61260
gcccaggcta gagtgcagtg gtgcgatctt ggctcactgc aagctctgcc tcccgggttc	61320
acgccattct cctgcctcag ccttccaagt agctgggact tgtacaggcg cccgccactg	61380
cgcctaattt tttttttttg tatttttagt agagatgggg tttcaccatg ttagccagga	61440
tggtctcaac ctctgcacct tgtgatccgc ccacctcagc ctcccaaagt gctgggatta	61500
caggcgtgag ccaccgcgc tggctgaaaa attctttttt ttttttttct ttgagacaga	61560
ctgtcacttt gttgccagg ctctggagtg cagtggcgcg atctcggtc actgcaagct	61620
ccgcttcctg ggttcatgcc attctcctgc ctccagcctc cgagtagctg ggactacagg	61680
gtgctcgcca ccacgcctgg ctaatttttt gtatttttag tagagacggc atttcaccgt	61740
gttagccaag atggctctga tctcttgacc tctgatccg ccctcctcgg cctcccaaag	61800
tgtctgggatt acaggcatga gccaccgcat ccagccgaaa aattctttta taatattcat	61860
atatataata taacgcacaa taaatacact gtctaaagaa agattcttta atattactat	61920
atatttatgt tatacaagta atagttttta aaagtcaaaa ccaaaagcag gttccagaat	61980
gttatatgca atacgatctc aattgtgtac aaaatgcatg agaaaataga aactggaaga	62040
aattatccaa acatgttaac catggaatta tgaatgattc ttattttctt tatattttcc	62100
ttcactttct gaattttcta taatgcatac acagaactct catgagaaaa tagtttttat	62160
aaaaaataca tcattaggaa caaatgaatg cagaacagac agaataatgg tgcagagtag	62220
ttttctctg catatggtag tttttttgtt gtttgttttt ttgagacaga gtctcgtgt	62280
tgccaggct agagtgcagt ggccgatctt tggctcactg caacctctgt ctcccgggt	62340
caagtgattc tcctgcctca gcctcctggg ttgctgggat tacaggcacg tgccaccatg	62400
cccagctaatt tttgtattt ttagtagaga cggggatttc accatgttgg cccggctggt	62460
ctggaactcc tcacctcagg tggctcgcct gccttgccct cccaaagtgc tgggattata	62520
ggcatgagcc atgagccacc ccgcctggcc tgcataata actttactgt tatgaatgcc	62580
tctagtttta tataacttca cagtttataa gatgttttca ttttaattctt acaattttta	62640
ttaatcccat agttcattgc ttttttgtaa ttttatctca gctgcctaaa aaatagtgtc	62700
aagagagatt gagagttaat tggaagaaat atacaatagg aaataagtga tgagcttggg	62760
tcagaaggat gcagtgttg acagtgttga ctctcatagg catggtatgt gcaatgatgt	62820
taatgctgta tttgttctat atccctctc catctctctt tagcaggtag ctaccaggc	62880
tactgctaag actcgtactt cccagtttgg tgtgggcagc tttcagactc cactcctctt	62940
cagctccatg tccctcctg gtgccccaac tgcctcgcct ggtgctgctg cctaccctag	63000
tctcaccat cgtggatcta actttgttga gtccagacca taaggagagt aacaggaaaa	63060
tcgcaccact aaagagaaag gatttggtag ttaaagttgt ttgcctgtgt tgtgggtaca	63120
ctgacctgat tgtagggaaa tgcaaggatga caatctattt agaattttta acctaccagc	63180
tgggtgcggt ggctcagcc tgtaatacca gcactttggg aggetgagge aggcggatca	63240
cttgagggtt ggagttaac ccagcctga ccaacatgga gaaaccctgt ctctaccggg	63300
tgtggtaccg catgcctgta attccagcta ctggggcggc tgaggcagga gaatcgctt	63360

-continued

aaccagag	gcagaggttg	cggtgagctg	agatcgcgcc	tttgactcc	agcctgggca	63420
acaagagtga	aactccgtct	caaaaaata	aaaaataaaa	aaaaaaaact	accacatga	63480
aaaaactttt	agcacatata	acaaaaatca	tgtgaatttt	tatacattta	atagtatgca	63540
catttaacct	aaatgagtaa	agaactctat	ggaaaggctg	cctggagaag	aagaattaat	63600
ttagggctga	gttttgagat	agaaaaggca	ttgattggca	gagagaagga	cagagttatc	63660
ctaggtaaaa	ttaatggctt	acctatagtt	gtttacttgt	ggcattagta	cacaatggaa	63720
ttgtgtagat	tggagtgtgt	tattcttctc	tgtgtatatt	ctagctcctg	agactggaca	63780
gactgcagga	caattccaga	cacggacagc	agagggtgtg	ggtgtctggc	cacagtggca	63840
gggccagcag	cctcatcatc	gttcaagttc	tagtgagcaa	catgttcaac	aaccgccagc	63900
acagcaacct	ggccagcctg	aggtcttcca	ggtaagagag	tgaagagact	ttcaaaaatt	63960
agaagctggg	agagaaagg	tccaggagga	ggagagacag	tgaaggagc	atgcctggat	64020
tgaggtgttt	ggttgggggt	atatgtgaga	agacagagag	ggataaatgt	agggatcact	64080
gtcagttatt	gaaaagattg	cagaagctag	atgcagtggg	gcttgtgtat	atgatgtcag	64140
cccttagaa	ggctgaagca	ggggatcact	tgaggccatg	agttcaaagc	caggctgagc	64200
aactagcctg	atcctgtccc	tgtcaacaa	acaaaaagg	agtatgaatt	gagtgtgata	64260
cataccattt	aaccagaaca	gacaaattta	gcaccatagg	aagatgcaa	agaaagttac	64320
tttagctcat	tcaaataget	ccatataccc	aagtcacagt	agctttgggt	ttaaagaga	64380
cagaatgatt	aaaaataaaa	agtagtgctc	gcttcagcag	catatatact	aaaattggaa	64440
tgaatataga	gaagattagc	atggcccctg	cgtaaggatg	acacacaaat	tcatgaagtg	64500
ttccatttaa	aaaattataa	aaagtaaatg	aatagaaca	taatgattat	agccataatg	64560
gtctatttac	acaagtcctg	agggactgca	agagtgaatg	gagttaattt	aggcaggaca	64620
aaggaagagc	tggtttaaa	caaagattga	aagaaagcaa	aacaggctct	ggtggaaaac	64680
aaataggata	agagactcca	tatatgtcta	taggggggta	tatgaaatac	agcaagcaga	64740
tttttctccc	ttgaaaata	ttgagaacta	ggaaaaggaa	aaagggtgaa	ctgtaggagg	64800
aagacagaag	ggattaggaa	aaaaggctgc	gatctaaagg	agtcaaagtt	ggtggaagta	64860
aggaaggcta	agagctcagc	acagcaaaga	ctcgggggta	gggatggtag	tgacggggaa	64920
tgggtgagta	gaacttggtg	agtgtgaag	atcaagggtg	gtgacccaaa	cttaattctt	64980
ttcttttata	aggagatgct	gtccatgctg	ggagatcaga	gcaacagcta	caacaatgaa	65040
gaattccctg	atctaactat	gtttccccc	ttttcagaat	agaactattg	gggtgaggat	65100
aaggggtggg	ggagaaaaa	tactgtttg	tttttaaaa	gcaaatcttt	ctgtaaacag	65160
aataaaaagt	cctctccctt	ccctccctc	accctgaca	tgtacccctt	ttcccttctg	65220
gctgttcccc	tgtctgtgtg	cctctctaag	gtaacattta	tagaagaaat	ggaatgaatc	65280
tccaaggctt	ttaggactgt	ctgaaaaatt	gaggtgggt	gaagttaaaa	cacctttcct	65340
tatgtctcct	gacctgaaat	tgtatagtgt	tgatttgtgc	tgagatcaag	aggcagggtta	65400
gaagaacctg	acatccactg	tttgcttg	atagtatggc	ttgtttttgg	aaagaaattc	65460
tgaagagagt	ggaggagagg	agaaatgtcc	tcatatttga	ggaccatgaa	acattgtagg	65520
tatatatggg	gcttttagca	gtttgagcat	aggctctttt	tgtgcctgtg	gagcagtcct	65580
tctggaagaa	aacatgtgag	taagtgagag	agagtgtgtg	tgtatgtgtg	tgtgtgtgtg	65640

-continued

tgtgcgacaca catgcttctg tatttcactc tttctcccta ttagggagtt atgcaaaatt 65700
tgccccgat tttaccttg tctttctgtg tacttttcaa agagtcctaa ggagttaaatt 65760
cttcaggga ttttccactt agtattgcag ccaagaata tttaaataaa cgtctttgct 65820
gcgcttgcat ccatgccag ccaatataca actgtaaagc aaatatagaa agtcggctgt 65880
tgatacgatt gtctgttato gaacacattc agtgataaag ctgggttact gctgcttttg 65940
gtgctctcac cttatctgga agatctgcaa acattaccta aataggctgg caagataaac 66000
actttctgga acccgagact tggccataaa gataatgctg catttttctg tcagaatcac 66060
atatgatgtg tgttctgtag aggttatttc tgcattgaaa ctcaacttct tggattagcc 66120
gtcccagtg aaatcctcat tgttggagtg taaaccaaatt acgaagccct cttgcaaagt 66180
agcctctttc atccatact caaaataccc agtttagcaa gcaactgaga tttagcttc 66240
tctggcccta agaggttttt cctctttgct cctccaatc ttgagattgg gttttgcttt 66300
agagtgaag tatcataatt ccgtatgata gatggggcct ggacacccat ctcaacaggg 66360
tcacttgga attaacaata gccatataaa tgcggataca gggtactacc ctccaccttt 66420
accttccca ggtaacagtc gtagatacca gctttttttt tttttttttt aaattggctt 66480
tggccagtag ctaaagtga agactgaatt aatgagaaga tatattaaat gtagtcatag 66540
gggactgagg agcaagggtg gccttgaaga ggccaaagga atgtccattt gctgagtttc 66600
ccttccttat gtctccagtc tgggtccagg tagtgagga aaaaaggaga cagtttattt 66660
ttttattcta tgtgcacact tacagtatac atatataatt ataccacaat ttacgaaacc 66720
aaaaagttga gtttccaatg gaaccctgt ttttaataa tcgacttttt aaatgtgatc 66780
aggactataa tattgtacag ttattatagg gcttttgggg aagggaggga tagcgagaag 66840
atgctctggg ggttttgttt ttgcttttcc ttcagggttt tatttttgac tgttttgttt 66900
tcttgttggc catttctgta ttgctggcat ctgtgctaag ctttacagtg gcaaaaataa 66960
tgacatgtag caaagatttt caaacaattt atttttccct tttgtaaaat ttcttgtgtt 67020
gtgtgatctt gattgcggct ttatcattcc tttccagttc ataacaaca ggcacccaca 67080
accagaggaa tctatagttt aagctccaga catacaaca taaggacat tgtgtcttta 67140
atttcaggaa tcagaaatca tagggttctg atcacattgc acgcctccc cctcacttgt 67200
cctcctgac ctgacacatt ctgagtaaca tcagcaggaa tgctctgacc atgagggtgg 67260
ggttttgggg tgggcgttgc ctgggttctt gggagagagg ggaagagtcg ggacttgaaa 67320
accactaggg cacatctgga tgccttccc cagtatgtcc tttctggat taaaatgagt 67380
gaaatttaaa ctgttcaagt ctggaacctg tttccctcta ggagactatg ttggttcatt 67440
agcaactttt tttttttttt tttttttgt gtgtgtgtgt gtgtgtgtgt gtgagagatg 67500
gagtctcgct ctgttaccga ggctggagtg cagtggcacg atcttggtc actgcaacct 67560
ctgccccttg ggttcaagca attctcctgc ctacagcttc caagtagctg gcaactacag 67620
tgtgtgccac catgcccagc taatttttgt gttttttttt tttagtagag atgggggttc 67680
actatatgtt ggccaggcta gtctcgaact cctgacctta ggtgatccac atgctttggc 67740
ctcccaaagg cctgggatta caggcgtgaa ccaactgcgc tagectg 67787

<210> SEQ ID NO 19

<211> LENGTH: 501

<212> TYPE: DNA

-continued

```

<213> ORGANISM: H. sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 217, 441, 498
<223> OTHER INFORMATION: n = A,T,C or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 217, 441, 498
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 19

ggagggagtg gtaatttaca aaggatgtga agtttccagg aaataggggg aaggaatta      60
cattatcttc ttgttctctg tctgccttat tagttctggt tcatgcttgc tttgcatgag    120
aaggttggca aaccttattt taactgctga gacttaagca tcaactaaac tgaataccac    180
attcttcagc agcacacttg gtatccatat cactctncct gctaccaaat gaccagatgt    240
gaccacctgg atgggggctt ctctttcttt ccatgcaggg aaaatcacag tgaaaattga    300
acggcggcga cggaacaaag atgacagcct acatcacaga actgtcagat atggtaccca    360
cctgtagttg ccctgggctc ggaaaaccag accaagctaa ccatcttacg catggcaagt    420
ttctcacatg aagtccttgc nggggaactt ggcaacacat ccaactgatg gtcctataag    480
cgggctttcc tcactganta a                                         501

<210> SEQ ID NO 20
<211> LENGTH: 2908
<212> TYPE: DNA
<213> ORGANISM: H. sapiens
<220> FEATURE:

<400> SEQUENCE: 20

cttgatttcc gcggtagcgg aggcggcggt caggcgccgc ttctggggag tggectttct      60
tttccctccc ctcccggttc ggtggcgcg gctcctccca ctgggggggg ggtggcgcg      120
cggcggtggc atctgcggcc atggcgcgga ctactgcaa ccccgctga tcttgactc      180
aagattctcc tgctcagac cccgagtagc tgggactaca gaaatgacat cagatgtacc      240
atcactgggt ccagccattg cctctggaaa ctctggacct ggaattcaag gtggaggagc      300
cattgtccag agggctatta agcggcgacc agggctggat tttgatgatg atggagaagg      360
gaacagtaaa tttttgaggt gtgatgatga tcagatgtct aacgataagg agcggtttgc      420
caggtcggat gatgagcaga gctctgcgga taaagagaga cttgccaggg aaaatcacag      480
tgaaattgaa cggcgcgcac ggaacaagat gacagcctac atcacagaac tgtcagatat      540
ggtagccacc tgtagtgccc tggctcgaaa accagacaag ctaaccatct tacgcatggc      600
agtttctcac atgaagtcct tgcggggaac tggcaacaca tccactgatg gtcctataa      660
gccgtcttcc ctcaactgac aggaactgaa acatttgatc ttggaggcag cagatggcct      720
tctgtttatt gtctcatgtg agacaggcag ggtggtgtat gtctctgact cctgtactcc      780
tgttttgaac cagccacagt ctgaatggtt tggcagcaca ctctatgatc aggtgcaccc      840
agatgatgtg gataaacttc gtgagcagct ttccacttca gaaaatgccc tgacagggcg      900
tatectggat ctaaagactg gaacagtgaa aaaggaaggt cagcagctct ccatgagaat      960
gtgtatgggc tcaaggagat cgtttatttg ccgaatgagg tgtggcagta gctctgtgga    1020
cccagtttct gtgaataggc tgagctttgt gaggaacaga tgcaggaatg gacttggctc    1080
tgtaaaggat ggggaacctc acttcgtggt ggtccactgc acaggctaca tcaaggcctg    1140

```

-continued

```

gccccagca gatgatgacc cagaggctgg ccagggaagc aagttttgcc tagtgcccat 1200
tggcagattg caggtaacta gttctcccaa ctgtacagac atgagtaatg tttgtcaacc 1260
aacagagttc atctcccgac acaacattga gggatatctc acttttgtgg atcaccgctg 1320
tgtggctact gttggctacc agccacagga actcttagga aagaatattg tagaattctg 1380
tcatactgaa gaccagcagc ttctaagaga cagcttccaa caggtagtga aattaaaagg 1440
ccaagtgtg tctgtcatgt tccggttccg gtctaagaac caagaatggc tctggatgag 1500
aaccagctcc tttactttcc agaaccctta ctcatatgaa attgagtaca tcatctgtac 1560
caacaccaat gtgaagaact ctagccaaga accacggcct acactctcca acacaatcca 1620
gaggccacaa ctagggtccca cagctaattt acccctggag atgggctcag gacagctggc 1680
accaggcgag cagcaacagc aaacagaatt ggacatggta ccaggaagag atggactggc 1740
cagctacaat cattcccagg tgggtcagcc tgtgacaacc acaggaccag aacacagcaa 1800
gccccttgag aagtcagatg gtttatattg ccaggataga gatccaagat ttccagaaat 1860
ctatcacaac atcaatgcgg atcagagtaa aggcattctc tccagcactg tcctgccac 1920
ccaacagcta ttctcccagg gcaacacatt cctcctacc ccccgccggg cagagaattt 1980
caggaatagt ggctagccc ctctgtaac cattgtccag ccatcagctt ctgcaggaca 2040
gatgttgccc cagatttccc gccactccaa cccaccccaa ggagcaaccc caacttgagc 2100
ccctactacc cgctcaggct tttctgccc gcagggtggc acccaggcta ctgctaagac 2160
tcgtacttcc cagtttgggt tgggcagctt tcagactcca tcctcctca gctccatgtc 2220
cctccctggt gcccacaact catcgctgg tgctgctgcc taccctagtc tcaccaatcg 2280
tggatctaac tttgctcctg agactggaca gactgcagga caattccaga cacggacagc 2340
agaggggtgtg ggtgtctggc cacagtggca gggccagcag cctcatcatc gttcaagttc 2400
tagtgagcaa catgttaac aaccgccagc acagcaacct ggccagcctg aggtcttcca 2460
ggagatgctg tccatgctgg gagatcagag caacagctac aacaatgaag aattccctga 2520
tctaactatg tttcccccct tttcagaata gaactattgg ggtgaggata aggggtgggg 2580
gagaaaaaat cactgtttgt ttttaaaaag caaatcttct tgtaaacaga ataaaagttc 2640
ctctcccttc ccttccctca cccctgacat gtacccctt tccttcttg ctgttccct 2700
gctctgttgc ctctctaagg taacatttat agaagaaatg gaatgaatct ccaaggttt 2760
taggactgtc tgaataattg aggctgggtg aagttaaac acctttcctt atgtctctg 2820
acctgaaatt gtatagtgtt gatttgtgct gagatcaaga ggcagggttag aagaacctga 2880
catccactgt taaaaaaaaa aaaaaaaaa 2908

```

```

<210> SEQ ID NO 21
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

```

```

<400> SEQUENCE: 21

```

```

acacacatat ctcaaggccc

```

20

```

<210> SEQ ID NO 22
<211> LENGTH: 20

```

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 22

aaggagcag aggactccct

20

<210> SEQ ID NO 23
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 23

caagatcagg ctgggaaaca

20

<210> SEQ ID NO 24
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 24

cccctaactt ggtcacctgt

20

<210> SEQ ID NO 25
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 25

actgccacac ctgtttcaag

20

<210> SEQ ID NO 26
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 26

taggaataat aacttatttc

20

<210> SEQ ID NO 27
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 27

actctcttac ctggaagacc

20

<210> SEQ ID NO 28
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 28

caagatggcg gcttcagcag

20

<210> SEQ ID NO 29

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 29

ggaaaagaaa ggccactccc

20

<210> SEQ ID NO 30

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 30

gccgcatgg ccgcagatgc

20

<210> SEQ ID NO 31

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 31

ggtacatctg atgtcatttc

20

<210> SEQ ID NO 32

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 32

cttaatagcc ctctggacaa

20

<210> SEQ ID NO 33

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 33

atcatcaaaa tccagccctg

20

<210> SEQ ID NO 34

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 34

tccgacctgg caaacgctc

20

-continued

<210> SEQ ID NO 35
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 35

catcatccga cctggcaaac 20

<210> SEQ ID NO 36
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 36

attttccctg gcaagtctct 20

<210> SEQ ID NO 37
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 37

ctgtcatctt gttccgtcgc 20

<210> SEQ ID NO 38
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 38

tctgacagtt ctgtgatgta 20

<210> SEQ ID NO 39
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 39

tttcgagcca gggcactaca 20

<210> SEQ ID NO 40
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 40

ctggttttcg agccagggca 20

<210> SEQ ID NO 41
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 41

aatgtttcag ttctgatca 20

<210> SEQ ID NO 42
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 42

agatcaaag tttcagttcc 20

<210> SEQ ID NO 43
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 43

ctccaagatc aaatgtttca 20

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 44

gctgcctcca agatcaaag 20

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 45

catctgctgc ctccaagatc 20

<210> SEQ ID NO 46
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 46

aaagccatct gctgcctcca 20

<210> SEQ ID NO 47
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 47

atcatctggg tgcacctgat

20

<210> SEQ ID NO 48

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 48

atccacatca tctgggtgca

20

<210> SEQ ID NO 49

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 49

agtttatcca catcatctgg

20

<210> SEQ ID NO 50

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 50

cctttttcac tgttcagtc

20

<210> SEQ ID NO 51

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 51

ctgaccttc ttttctactg

20

<210> SEQ ID NO 52

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 52

agactgctga ctttcctttt

20

<210> SEQ ID NO 53

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 53

tccattctg catctgttc

20

-continued

<210> SEQ ID NO 54
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 54

agccaagtcc attcctgcat 20

<210> SEQ ID NO 55
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 55

gcctctgggt catcatctgg 20

<210> SEQ ID NO 56
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 56

gggagaacta gttacctgca 20

<210> SEQ ID NO 57
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 57

cagttgggag aactagttac 20

<210> SEQ ID NO 58
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 58

ctgtacagtt gggagaacta 20

<210> SEQ ID NO 59
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 59

catgtctgta cagttgggag 20

<210> SEQ ID NO 60
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 60

ttactcatgt ctgtacagtt 20

<210> SEQ ID NO 61
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 61

tcgggagatg aactctgttg 20

<210> SEQ ID NO 62
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 62

ttgtgtcggg agatgaactc 20

<210> SEQ ID NO 63
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 63

caatgttgtg tcgggagatg 20

<210> SEQ ID NO 64
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 64

tagccaacag tagccacaca 20

<210> SEQ ID NO 65
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 65

gctggtagcc aacagtagcc 20

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

-continued

<400> SEQUENCE: 66

ctgtggctgg tagccaacag

20

<210> SEQ ID NO 67

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 67

acaatattct ttcctaagag

20

<210> SEQ ID NO 68

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 68

atttcactac ctgttggaag

20

<210> SEQ ID NO 69

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 69

acttggcctt ttaatttcac

20

<210> SEQ ID NO 70

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 70

acagcacttg gccttttaat

20

<210> SEQ ID NO 71

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 71

gaacatgaca gacagcactt

20

<210> SEQ ID NO 72

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 72

gttcctcaca ttggtgttgg

20

-continued

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

<400> SEQUENCE: 73

ctagagttct tcacattggt 20

<210> SEQ ID NO 74
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 74

ccatctcttc ctggtaccat 20

<210> SEQ ID NO 75
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 75

ttactctgat ccgcattgat 20

<210> SEQ ID NO 76
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 76

gagatgcctt tactctgatc 20

<210> SEQ ID NO 77
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 77

tggaggagat gcctttactc 20

<210> SEQ ID NO 78
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 78

agtgctggag gagatgcctt 20

<210> SEQ ID NO 79
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 79

gaaattctct gccggccggg

20

<210> SEQ ID NO 80
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 80

ttcctgaaat tctctgccgg

20

<210> SEQ ID NO 81
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 81

agaccactat tcttgaaatt

20

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

<400> SEQUENCE: 82

ggacaatggt tacaggaggg

20

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

<400> SEQUENCE: 83

tggctggaca atggttacag

20

<210> SEQ ID NO 84
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 84

gtctcaggag caaagttaga

20

<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 85

cactgtggcc agacaccac

20

<210> SEQ ID NO 86

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 86

ctggccctgc cactgtggcc

20

<210> SEQ ID NO 87

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 87

ggctgctggc cctgccactg

20

<210> SEQ ID NO 88

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 88

ggaaacatag ttagatcagg

20

<210> SEQ ID NO 89

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 89

caatagttct attctgaaaa

20

<210> SEQ ID NO 90

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 90

tcacccaat agttctattc

20

<210> SEQ ID NO 91

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 91

tattctcacc ccaatagttc

20

-continued

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

<400> SEQUENCE: 92

agaggaactt ttattctgtt 20

<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 93

aagggagagg aactttttatt 20

<210> SEQ ID NO 94
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 94

atccaaggca aacagtggat 20

<210> SEQ ID NO 95
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 95

gtccaggccc catctatcat 20

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 96

tgaaaatcctt tgctacatgt 20

<210> SEQ ID NO 97
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 97

ccaggtggtc acatctggtc 20

<210> SEQ ID NO 98
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 98

tgagtccaag atcaggcggg 20

<210> SEQ ID NO 99
<211> LENGTH: 65001
<212> TYPE: DNA
<213> ORGANISM: M. musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 14965, 14966, 14967, 14968, 14969, 14970, 14971, 14972,
14973, 14974, 14975, 14976, 14977, 14978, 14979, 14980, 14981,
14982, 14983, 14984, 14985, 14986, 14987, 14988, 14989,
14990, 14991, 14992, 14993, 14994, 14995, 14996, 14997
<223> OTHER INFORMATION: n = A,T,C or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 14998, 14999, 15000, 15001, 15002, 15003, 15004, 15005,
15006, 15007, 15008, 15009, 15010, 15011, 15012, 15013, 15014,
15015, 15016, 15017, 15018, 15019, 15020, 15021, 15022,
15023, 15024, 15025, 15026, 15027, 15028, 15029, 15030
<223> OTHER INFORMATION: n = A,T,C or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 15031, 15032, 15033, 15034, 15035, 15036, 15037, 15038,
15039, 15040, 15041, 15042, 15043, 15044, 15045, 15046, 15047,
15048, 15049, 15050, 15051, 15052, 15053, 15054, 15055,
15056, 15057, 15058, 15059, 15060, 15061, 15062, 15063
<223> OTHER INFORMATION: n = A,T,C or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 15064
<223> OTHER INFORMATION: n = A,T,C or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 14965, 14966, 14967, 14968, 14969, 14970, 14971, 14972,
14973, 14974, 14975, 14976, 14977, 14978, 14979, 14980, 14981,
14982, 14983, 14984, 14985, 14986, 14987, 14988, 14989,
14990, 14991, 14992, 14993, 14994, 14995, 14996, 14997
<223> OTHER INFORMATION: n = A,T,C or G
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: 14998, 14999, 15000, 15001, 15002, 15003, 15004, 15005,
15006, 15007, 15008, 15009, 15010, 15011, 15012, 15013, 15014,
15015, 15016, 15017, 15018, 15019, 15020, 15021, 15022,
15023, 15024, 15025, 15026, 15027, 15028, 15029, 15030
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 99

agataagggt cactgggtgag ccttccaatt cgggattgta gttcattcca aatattgtca 60

agttgacaac caggaatagc cactacacat ggcttttttt actacatgat tatagggtga 120

atcaacatgt ctattatata ctaaaaaaaa aaagttttta accatgactt ttgttttgg 180

ttttcaacac atagttttctt tgtgttaatc atcctggctg ctttagatct taattttag 240

acctggctgg catccaactc aaagagatcc attggcctct acctcccaag tactgggatt 300

aaaagcatgt aatgccatg aactacaatt tcttatatta aagtgtgcca tatagatgtc 360

atgtttttgt ttgtttttgt ttgtttttgt aaatttgaca caagctaaga tcatctgaga 420

ggaggaaaag ccattaaggc aatgcctcca tcttggcata gtggtgcccc cctttaatgc 480

cagcaaatga aagtgtgaaa gcagggtgat ttctatctgt tcacaactgt ttgaaactcc 540

agggttaatgg gatcttttct gtctgtctaa ttgtgttcca atactcaggt gtactgactt 600

-continued

aaatgcagac acattcacat aattaaaaat aaaactattc aaaaccccaa gaaaatgtct	660
aaacaaacca accaaacca ccaataacc taaagcaagc aagcaacca caaacgagaa	720
gccagcatga tgctactgcg cctctcactg cacctctttt tagtgaatgg gagttagttc	780
tctctcga ccatgtgtg gcttttggag aatccaactt caagtacctt tagctcttga	840
gccatcttgt cagttctact tctaatgtt tttaaaattt ttgtgtatgt gtgagtgcac	900
atgttttgg gtgagaaaag ttgaagataa ttgcaggag tcctctcctt gtgtaagttc	960
agagcattgg atcttgggat gttaggtgta gctgtgtagt ggagtcgtct ttatggctaa	1020
ttaaaaaat ttttttggat gaatcagact gacaacaagc caaagagtag tgccatatgc	1080
ttatagtctt aacattggaa ggagaggggtg aattcaagac ctttttcac ctcatatgtga	1140
atttggggtc agtctaggct acatgagacc ttgtttcaaa gaacaaaatt accctcctcc	1200
ccccagtcca catatacatg gtgatgaata taatagactt tgggtgttag ttccattcac	1260
tttgcttctc actactggat taatttgcaa ggtggccttt gtttcatgctc ttgggttttt	1320
gtttgttttt gagatagtgt ctttctatat atagctcctg ctgtcttaga actcactatg	1380
tagaccaggc tggcattgaa ctcagagaaa ttggccagtc tctgcctcct gagtactagg	1440
attaaaggca tgcataccta tgcctggatc tgtttgtagt tctttttttt ttttaatat	1500
atatttttaa gatttattta tttattttat gtatatgagt acactgtagc tgtacagatg	1560
gctgtgagcc ttcattgtgt tattgggtat tgactttagg acctctgctt gctccaatca	1620
acctcgccca ctccagttgg tcggctcact cagttcctgc tttctctggc ccaaagattt	1680
atttattatt cttaaataagt acactgtaat tgtcttcaaa cacaccagac gagggcgtaa	1740
gatctcatta ggggtggttg tgggccacca tgtgggtgct gggatttgaa cgcaggacct	1800
ctgaaagagc agtcagtgtc cttaccgct gagccatctc tccagcccct gcttgtagtt	1860
cttgatttgt aaaattatag aatttatctc acagtgtttt gagtcgacat tgtctgttct	1920
gaattgctca gttcttataa ttagacatta cgtctgtgtg ttactacct tgctatttta	1980
aaaaaacttg tgacatagga cacctcactt ttggagggca gagaaaggga ctagtttcat	2040
ttttagtagc agactggtct ttgcattctg agttctggaa tacttgttta ataaaaattc	2100
tttgttcgtt gtctccattt caaatgttgg catctttggt accacgtaat caccagctt	2160
tttctacca gcttcagagc caactcttaa gaattagtta tcggactttt actagtgaca	2220
aaagttcata aagaaaaaac aacctagaat ggattagtga tcctgtgtt agaacctata	2280
aagagggttt gcataacaaa tcgtctgtag gaagcatatg ctgatgagcc cactaagaaa	2340
gaaaacattt tagtaaaatg ctgcttttct ttgcatttca ctgacgtcaa tttggttatg	2400
aatctctgac gccgagaagg ccggattagg gaaacagctg gttggcttcc tagctcaggc	2460
ttcttagcac tctcgggtc accggactca ctggccgagt cactagcccg gcctctatgg	2520
cgacttactg tttctattgg ccagttctcc caggagggt gtctggagac tgaccgcgcc	2580
catagttttg ggcgtgtctt ctgccaggga tggggagggg ggtgggcgtc cgccatcttg	2640
gattccgcgg tagcggtggc ggcggtaagg tgcctaactc gcggagtggc tcttccctcc	2700
cctccccag ctgggtggcg gctgcccctc ccaccgaggg tggcgaggg acggtgccat	2760
ctcgaccatg gcggcgacta cagctaacc aggtgaggcg gcagaaagga ctgacaagtg	2820
cggagagcca gagcagagca gcagggccgt ggcgttcggg tgttggggga ggggtgtcga	2880

-continued

ggaggcgccc	tgcccgagg	acctgggaa	cggtgacgg	gtgtttggg	gctccgtgcc	2940
ccaacttctg	gagtagtgg	ggcgcttggc	cagcgtctcc	actctgcctg	cggtgttagg	3000
gagtgttgtg	gtcttttaac	cctctgccag	ctgatgttcc	cctgatgcct	agtaagtaac	3060
tgggcaaaact	gacttggtgt	aactgcgagc	gtaaaactggg	ctatagacgg	ggccacgttg	3120
acgttttgca	aagtcttgct	tgattctaca	cttggtttac	atttaaattg	aaaacttagt	3180
tctttgagaa	tctgtcaga	ttcttgtaac	tcctatactt	tgaaatttag	ggtttttagcg	3240
tagttatttag	tgtcttgctg	ctgaaggcag	aggtttggtg	aatggtaata	gttcaggaca	3300
ggtctttagt	ccagaaccca	ggtttaaatc	ttgttaggtc	gaggtggagc	aactcctgtt	3360
ctttcagaaa	aatgtcccgc	gccatttgtc	tgtggacgtc	ctcttgcttg	tttgtctgtc	3420
tgtctctgtc	tctcgttcac	cttattttga	gtcttgcttc	attccagccc	ccggttgact	3480
ttggatcact	gcagtctccc	tctcagtcct	ttctactgta	ttcagttaca	tcttaggaag	3540
tatttcattt	tagttgggct	aatttacctt	gttattttcc	aacaaagtaa	atccatcatt	3600
tcccagaagt	ctgtatcatc	gaagagtgtg	gagggagggt	tgtgtaatat	tggtctctgc	3660
tatttcacat	tgaactttta	aattttatct	tgttaatgta	ctatattaca	gtaacagggt	3720
acacacacgt	atgtatatac	atacacacaa	tagctgaaac	actgggaaat	gtattgtttt	3780
cccattattt	ttggaacag	cctttttttt	taagagagag	agagagagag	agagagagag	3840
agtcctagaa	cttatatgta	gccaggttg	gcttcaaatt	catgtgtcaa	tatcaacttt	3900
aaaaaaaaata	tttttaagct	ttagaaatta	tgtatatgat	aatgtctact	tgtgagtgca	3960
ggaatgggag	gagtcagaa	tagggtgttg	gatccctgc	agcaagagtt	tcaggcagtt	4020
gaaagccccg	tgatgtggat	gctaggaact	gacattaggt	cctagaagag	taacacatac	4080
tcacaactac	tgaaccttcc	tttcagcccc	tgaatatcag	ttttttaaat	cctaaattat	4140
tatttttttt	acatgaagat	gaagtaaatt	gtcaggaaac	tattggaata	ttgatgaat	4200
tatagaataa	aactatacaa	ctgaaaaatg	ttagagaaaa	tcagaccttg	tagcaaaata	4260
gccccatgtc	gattagagta	aacaagattt	caaactgac	ccatgttgca	aaatccttat	4320
ataactcttc	agactgcaaa	gtgtctctct	tgttaaggcc	gtagagacac	gttagtaagt	4380
cagaagcttt	tctagctgcc	ctgttctgat	tttaaaccac	ttactaaaac	aacactttct	4440
tgaccaaata	gtcatttctc	tatcaatatt	agcttaagtc	tgtaagcagg	aaatagtaat	4500
ttttttctat	ttttttttct	gagtgaggaa	ttttgagagg	ctggcctgca	gtgttctgtg	4560
aagatcaggc	tggccttgaa	cttgacgtgg	tcttcttgct	tctatcttca	agtgcctgaa	4620
tcactcgcat	gtgccatcct	atataaaact	tcaaaacttt	ttaaaaagta	cgatttaaga	4680
atctttttta	atgaaacagt	tgtttgtttg	tttgtttgtt	tgttttgact	ttggtttttc	4740
aaggcagggc	ttctatatgt	atccctggct	gtcatgaaac	tcactctgta	gaccaggatg	4800
gcctccaact	caagatctgc	ttgctcctgc	ctcctgagtg	ctggattaaa	gctgtgagtg	4860
tcatcaccag	tagaaataat	tgattttatt	tattgttatt	tgattgcttg	cttcttcaat	4920
tttgagggtg	gcagagtcat	cataggtact	taccaaacag	agggagaata	ggctggaatt	4980
cctttaatct	ttgcagaagc	agggggatat	cttagttcat	ggccatcttg	gtctacaaag	5040
tcagttccat	gtacatagtg	gagaccttgt	ttcaaaatca	aaagccagac	caaaccaagc	5100
aaaaacctca	aaagggtgagg	tgtaggttct	tagcaaacct	ttgaaaatta	acctgagaat	5160

-continued

gtaagagttt tcttaaattc tagtctgctg ttagttatgg catagcaccc agtgggttcct	5220
gctgtagctg acatccctgc gtagcctcag cctcttatga gatgggatgg taggtctgag	5280
cggagaacag agaacgacag acccagttag actaaccccc tgctctcttt accatctgcc	5340
ttaacttcct tttccggggg ctacattcct agctcaagat ttcttttttc catgtggaga	5400
attcttccat gtcttctaatt ttattgatcc catgttcagt acatgcatga tacttaagtc	5460
ataaaataga gccttttgtt gttgcttttt cctccttcct ttttgtgtca aacaggatat	5520
gttttgccct gttgaatttt ggaaaattag attcaccact ggaggtatat acagtgggaa	5580
attactatgt tcagtgtgca cttgtacaca ggccagaaga caccggatat ccacctctgt	5640
aactttctgt cttattcctt tgaggcagaa tttcttctta actgtgggca tcttactgtg	5700
tcactctgcc ttatttcttc caggtcaggt gtctccctta acctgaggtc tgtgtgtttt	5760
gctcggctga cagtcagcaa ggcctagcag tcttctgcc ttggatcctc agagtgcattg	5820
gattcctggt ggatgcagga tgatgccaga cttgttatgt gggttctggg atccaaactc	5880
aggtctccag attgtgtagc aagtgtcttt aacctctgga tcattgtctt attccacatc	5940
ccacctccgc tttttgagac aggatctgtt actggcctgg agtgggcaa agaggataaa	6000
cttctgggta gagagcccca agctcactgg gtttcggctt taccaatgct ggaaatataa	6060
gtaaagccta ccattgcttg tcttttcatg tgggttcttg agattaactc aggaccttat	6120
tgcttgattg gcaattcttt tttgattgag ctaccaagcc ctttattatt aattagtcag	6180
tgttcttaat tgctggtcat atctccagcc ccactttccc cccacccccc cccaaaaaaa	6240
gattttaatt aaattatgca cattgggtgta gtagttactt tctgtggcc atgaagagac	6300
acatgacca tgggaactta gagaagcatc gctttattag acttgagttt tccagagggtg	6360
agtccatgat cactgtgact ggaagcatgg cagcagctgt attacttcca acaaagccat	6420
acctcttaat tcttcccaag aactaacac caactgtgga ccaagaatta aaatatagga	6480
gcctgtgggg accattctca ttcaaaagac cgtaattact gcatgtatgt ttgttcatgt	6540
gagtgcaggt gcagaagagt gtgttgattc tctgttagtg caattacagg tggttgtagg	6600
ccatctaagt tgggttctca gaactgagct catgtgttat gcaggaatgc caagttgtct	6660
taacaactga gccatctctc cagcccccca aatcaatcaa tttatctctt ttttttttct	6720
ttctttttaa aggaattgaa ccattttact aactcagcag ttaaaatata ataaactttt	6780
tgtttttgag gcaagctcga ttttagactag gctaggttga aactcactat gtctctgagg	6840
gtgacctga atttcttttt ttcatttttt aagatttctt tctttttttg tttttttgtt	6900
tttcagagca gggtttctct gtatagctct ggctgtcttg gaactcactc tgtagaccag	6960
gctggcctcg aacttagaaa tccgcttgcc tcttatttct tgatattgag tacactgtag	7020
ctgttttcag agacaccaga agagggcac agatccatt acagatgggt gtgagccacc	7080
atgtgggttg tgggaattaa acccaggacc tctagaagag cagtcaatac tcttaaccgc	7140
tgaactatca tctctccagc cctgatctta aatttctgat ccaagtgtga tgatcttata	7200
gttacaacca tgctgtctt accatgtgct atggatggag ccagggttg gtgcatgcct	7260
ggcaagcatt ctaccaactg aactgcatac tcagtggata acagtgttg aacgaaactt	7320
cagtgggtgt acttttatgc agtagacttg tggtagcaag tttgactcta ttttctaga	7380
atttaagaag taaagactta cgttgagaat ggtagccgtg tatcagtaaa caaaaatggc	7440

-continued

tgagagtggtg	ttctgccatt	agaagcaagc	actggctgct	cttggagttg	actgaggttt	7500
ggttccagca	catactgggtg	ctactacca	cagctataat	tccagtagat	ctattgccac	7560
cttctggcct	ccatggacaa	caagcctgca	tgtgttgcat	atatacacac	aggcaaaaca	7620
tacacataaa	gtcgttttaa	atacaaaata	gagaaaagtt	ctctgatggt	acaatattat	7680
aaagaatctt	gaaaaatggt	tccattattt	gtccagtggt	ttgtcageta	tataactgat	7740
ttcatccaga	tgttgtaata	ataaaagaat	gtctttaaca	cccccttgaa	aatgtaggct	7800
tgaactcagc	agagtctgag	ccaactcccc	aacctcagg	tagtaggcac	tgcttgata	7860
acctggttga	attgcttgac	ttgctgtttt	gacagggctc	gggtgtgtgg	ttcaggtctg	7920
acttaggctc	tccatctctc	ctgagtgttt	aagagatgga	catgagaacc	tcagctgggt	7980
agttagttca	aggccacttc	tgggtctacat	gagactgcct	cagcttcccc	agtactagga	8040
ttataggcat	gacctaccat	gccttgctaa	atccatctat	ttttaggatt	gctgtcctat	8100
tttccatgat	gacttcagta	ggtaaatatc	agggagttag	tccattgtaa	ataaacacgc	8160
actgtcctaa	agggtctcag	tgccagcaaa	gatctgtgaa	ttctgagggc	agacaaaact	8220
atacagcaag	agagaccatg	tctcaaaaca	ataaaaacaa	aggatgataa	ctctttgatt	8280
ttatagcaag	gaaacaaacc	tagagaaaga	aatgaacata	tttattaagt	atttattatt	8340
tttctctgtg	tccaggtcat	acttttagtat	tttgttggtt	actcattata	ttatttattt	8400
ttaaaatatt	tatttgcttt	atgtgtatat	gcgtgcctga	gtgtatgtct	gtaccacatg	8460
ggtttagaag	acttcagagg	tcaaaagagg	aggacttttt	aagtccccctg	gaactggagt	8520
tacagatggt	tgtgagccac	catgtgggtg	ctgggaattg	aacctgggtc	tctgcaagaa	8580
cagtcagttt	cttaaccctc	gagatatctc	tgtagtctct	attctctgta	tcataaagtc	8640
tcttctat	actcctccca	caatttttaa	aactttatac	cttccttcta	agcatggcgg	8700
tgacacccat	taatccgagc	acttgggagg	caaaggcggg	tggatcagtg	cgagttcaag	8760
gctagcctgg	tctacaaatc	cagtctagga	cagccagggc	tgttacacag	agaaaccctg	8820
actccaaaaa	caaaattata	ctttaacttt	tatatctctc	cttttcattt	ttacagtagt	8880
tgggtgacca	cagtaagttt	ttcctgagac	aggctctcaa	ataccatgct	ggccttaatc	8940
ttactatcct	aagctagggc	ttgaacttcc	agaccctact	gcttatacct	ctgtagtggg	9000
gggattagag	ttaggtgccca	tcactccagg	gctattgggc	tcaagatagg	ggcttcatgc	9060
ctgccaggca	aatacctagc	tgagctacat	gggttccagg	tcagtcagaa	ctagggtgag	9120
gtcctgtctt	aaaaaaaaat	aataataata	aaattgggoc	agggatgcag	cttagttaga	9180
agaacccttg	tgtgtcagat	acaagatcct	aagtctcatt	cctagtacat	tgcaaacccc	9240
acctccctcc	aaacacaaaa	gggtttctaa	gctggataag	gtggtggcct	atatctgttt	9300
tttctttgtt	ttttcctttg	agaacgagtg	taatttagct	ggcctaaaaa	ttcatgtgaa	9360
cttctgtgga	ttctcctacc	gtctcctcag	tgctggaatt	acaggctaca	ctactgacaa	9420
agcaagtccg	ttctgtcaga	agattccttc	agttgactgc	ttttttcata	tatatattagt	9480
ttttcatttc	ccatgaaggg	ggagtcagta	ttttccattt	ttttccatgt	gagttgatat	9540
cagtaaacct	taagttcaga	tatgtaaatg	catatatatg	tgtgtagaca	aacaactcca	9600
tcaacttttg	tgtctgtttt	tgagacaggg	tcttaccatg	tagcttttagc	tatcctcgat	9660
cttgctatgt	ggaccaggct	ggtctagaac	ttaaattaac	ctgcttttgc	ctcccattgt	9720

-continued

ctgatattaa aggtatccac caccctatct agtaattttg ttttttagac ttatttttta	9780
attgtatata tgtatatgtg agttcaggtg cccttgaagg tcagaagagg tgttgggtcc	9840
tctgggtgctg gagttccaga ttgagcttcc aggtgtaggg aacagaggaa gtccctgagta	9900
actgcattgt tgacatgcac gtggccatat tgaggctctc aagggcacag acccatggga	9960
gattgacaaa gccattaccc atatggccag gctaaagaga gtgacaaagc tcttctgaat	10020
tctagtatga gtgtgttagt gtgtgcttac atgtgtataa atgtatgtgt gtgtatgtgc	10080
gcatatgtgc gcgtgtggag tctggcttcc cctcatccgt ctacctctct taccctgaagtc	10140
tgggggttta tatgtgtgcc actatacctg cctttagatg gactaactcc tatttggtaa	10200
tcttttgtaa agtatttttag tatcagtttt cagaaagaat attgggtttat aattggcata	10260
ttttttactg tttgttttgt tgtgatatca gattaatact agaatcatca gtaaaatgag	10320
gccaggagag gatatacat ccaaatattt tcttgaagag actatgtaga actcatagta	10380
aagtaatttg aacctggata tttctttttg gactacagtt gtagaactat tattattatt	10440
attattatta ttgagacagg gtttctcttt gtagccctgg ctgtcctaga aattactctg	10500
tagaccaggc tggctctgaa ttcaagagat ccacctatct ctgcctctgg gcttaaagtc	10560
gtgcaccact gctgcatggc tattacattt gtttatttat ttttatattt agtcagttat	10620
aattgtatgg gcttttctta gtgtgtgttg tcttgaagta aaagcttaat gattgatttt	10680
gttttgtttt ttaagatgta tgtgtgtgtg tgtgtctgtg tgtgtctgtg ttattatata	10740
tatgtgccct tggagggcag aagagaaaact ctggaactag agtttcaggt gactggatta	10800
tctgccgtgg tgctagggat agaactttgg gcttttgtaa gggagccatc ttgetaacc	10860
tttgctttgt tgctttttgt tttctgtgat acagcagtggt tgtaaattgc ttaccaggta	10920
gagttttaat tgtctcccgt aattttaatt ttgctatatt gtatttaaat tttttgttta	10980
ttgttggtat tattctctct cctctccctc ctctctctct tctctctctc tctctctctc	11040
tctctcttgc tctctctctc tctctctctc tctgtatgcg tgtgacacat ttttctaagt	11100
cagttttctc ctactgtggg ttcaagggca gaactttgat cagatttgca tggctggtag	11160
ttttctctc tgagtcacac tgtcagctct ctagtatatt tttgttttat gcaactgtgc	11220
atatctgtgt atgtgcttg agtgacgtgc ccttagagac caaacaagga tgtaggatcc	11280
tctagagcaa gaggtacctg tgtttgtgag cagcccaaca tgggtgcctg aagaactctg	11340
caagagcaga gcttgtgcct cacttacatt tagttaagct tgtgacagtt ttcttttgag	11400
actttgactc attcattaat tgtattgtat ttttttcatg tttgtagaga ttttctatc	11460
tttttcttc cttctttctc tcttctctc cttctctctc tcttctctc cttctctctc	11520
ttctttctt ctttttttga gacaggggtt ctctgtgtg ccctggctgt tctgaaactc	11580
actctgtaga ccaggtggc ctcaaactca gaaattcacc tgctctgctc tcccaagtgc	11640
taggattaaa ggcgtgccc accatgccc gctttttttt tttttttttt aagatttatt	11700
tatttatttt atgtatttga gtcagatgat cgtgatccat catgtggttg ctgggaattg	11760
aactcagacc tctgctcgt ctaaccctaa gatttattta ttgttatatg taagtacact	11820
gtagctgact tcagacactc cagaagaggg caccagattc cattacggat ggtggtgaga	11880
cacctgtgg ttgctgggaa ttgaactcag gacctctgga agagcagtta tatctccaga	11940
tataatgttt ttcttttagt tgtgtcagat tttacaacac attttgccct gtcttggtta	12000

-continued

gtatatgtgc attgctgtgt tactggtggt ggattctcac tctgtaattt cttcaggtaa	12060
attttatattg ctgttttttt ggtttttttg ttttttttg tttttcgaaa cagggtttct	12120
ctgtatagcc ctggctgtcc tggagctcac tctgtacacc aggagccct cgaactcaga	12180
aatctgcctg cctctgcctc ctgagtgtcg ggattaaagg cgtgcgccac cagccccagc	12240
ttatttgctg ttttatcggg tttatttgta tatataacaa ttcctataac cacagcttta	12300
ggaaaaaaag cttggtctct ctgtgtcccc tggctaggct cagtcaccta acccaattaa	12360
ttgacaacta atgatgaaat acagagattt actcattgtg gtcacattgt cctaggaaca	12420
gatagaaggg tccagtgacc cctaagtccc tttaactata ttgacttcag ctttaggttt	12480
aagtagaaca gttagggcag caggccggag gtttagccag tcctgaacac agtgtctcat	12540
tgtctcgggt cctgctaggt ggatgaatta aattgttgct gacaggacca ctgtggctcc	12600
tacaagatag tgcattctgg gtgtagcctc ttcacacag gtaattgttc tcaactgtctc	12660
agccgaggca tagcttcagt tctttatctt gtttctgctg gaatccaagg tgacaagaag	12720
acagattaaa gacagtgacc tagctctgtg tctccagaag taaaggagac agacagacaa	12780
aacggaggcg gagatgccag cctttcatct tacttttagta aagcaaaggc tcacattggt	12840
ctttgcaaga gtaacttctg tcttagttag gttttctggt gctttgatga aaactttata	12900
tgtgacaaa acatgttggg gaggaaggat ttatttcagc ttatacttcc acatacacat	12960
cacagtccat cacttaagag agtccaggca ggaactcagc agggcaggat ttggggacag	13020
gaaactcaagc agaaatgact tggtttactg gcttcgtctc ccatggcttg ctcaacctgc	13080
cttcttatag caccaggac caccagccca gggatggcat tacctacagt gaactgggccc	13140
ctcccatatc aatcactaat taagaaaact ttccacaggc ttgctgcat accaatctag	13200
tggggcattt tctcagttga tgtccctgtt ttcagtgact cctttgtcca gttgacatga	13260
agcatagcct ctaaggctgt tgcagtccca cttaactttg gttaatgtgt gcatgatgtt	13320
cctttccttt cccctttctt tctttttttt ttttttaag atttatttat taatatatgt	13380
aagtacactg tagctgtctt tagacactcc agaagaggga gtcagatctt gttgcggtatg	13440
gttgtgagcc accatgtggt tgccgggatt tgaactctgg accttcggaa gageattcgg	13500
gtgctcttac ccactgagcc atctcaccag cctcctttc ccttttcctt tccctcctt	13560
tcttttcctt tcctgagggt gagcaccgag gatgactttg acccccagc cccgagtgtc	13620
ggagttatac acccagagcc tctagcatgc taggcccata ttctactggc tgagccatac	13680
tccaagcccc atgctgtgac acagggtggg tccctttagc aagttcttga tctcatggat	13740
aaaagattga agaggctaga gagatggctc agtggttaag agcctgcatg actcgtccag	13800
aggatctgag cttggtttca agtgccatt atcagggcaa ctcccagctg actgtgcagt	13860
gccctctttg gcatccgtag gcagcagcac tcacatgtgc acacatcctc ctcaactctc	13920
cccaccacaa taaaaataaa tccttttaaa aaaatgtgct ttgaagggtat tattttacta	13980
gagtcagtaa gaaaaggcag ggcaggcaag ctagagatct cagcattgtc atgaggaagg	14040
aaatgtaaa aagacaaaaa ggaaaaagtc acatccttaa atagaacagg aggaaaaacga	14100
cctcttgggg gacaggtgac tcacggaaga actggggtat tcagagccca tcacaaaact	14160
gccctccttg gtagacgtac tttatggggc ggtctcactg cagcccaggt ggcctgggat	14220
tagcagccat cctgaacgct gcttttatag accagaagct ctacacttg atggaatatg	14280

-continued

taatactact	tggtttaggt	ttgtaatcag	tcaagagttg	ctctatgtgg	cctaggactc	14340
agatgtgttt	aagattagaa	agaataataa	ctgtatgtag	tgttgtagc	ttagtgtcta	14400
gttttattag	ctttggatca	ggaagggatg	aataacagtt	ttgaactatg	tcaatttacc	14460
tttaaaatgg	tttacaatt	tgtttatggg	agttcttaca	tgtgtgtgca	cacatacatc	14520
agaggacaac	ctcaaatatt	gttccttaga	gtagttcacc	ttgttatgtg	agacagtctc	14580
tcattggcct	tgaacgtata	acaagatggc	cagcttgtct	acttggtttt	acctcccagc	14640
ttctacatca	gtgctgggca	tctgacctca	ggctcctatg	ctattatggg	aaacactttg	14700
ctgtctgaga	catgtctctc	taatcccagt	ttacctgttg	gcaaaggcta	gttttggact	14760
aatttgaagc	tctgtcatt	ggctcatttt	aaattttcct	tagtttttgt	tttgttttgt	14820
tttgagagtg	tgtatgtgcc	catcttgatg	aaggtacaga	ggtcagagga	cagcttgccct	14880
gagttagggtg	atcaggggtcc	tgctcagtct	tggcaggaag	ctcccgcatc	tgtaagcca	14940
ttttcctagc	cctcaaaacc	tgagnnnnnn	nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnnn	15000
nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnnn	nnnnnnnnnn	15060
nnnntcttgc	ttctctgggtg	ctctggttca	ttctcattga	tgcccatgat	ctattgataa	15120
gatcatatga	catttttatt	tgaattatac	atatttctat	acaatacagt	ccctactttc	15180
ttccctccca	tccacacttg	ttttcccat	cctgttaaga	tggctctgct	atgetggcct	15240
taaactaggt	agctagcata	ggttgacctc	aaacatgcag	gccctttgcc	agtctcccga	15300
gtgtcaacat	tatagggatg	caccgttatg	cctggttcac	ttacagcttt	tattcccaaa	15360
gttcccat	ttccccata	ttctatgttt	ttatttgcta	agactgttta	acatttgttt	15420
caaatgttct	tctaaatact	tgctgaagaa	ttttatcag	ggctacttgc	aaaacttttg	15480
ttagataa	ctaacatctg	tattgtctta	gtgttggeat	ctattagctg	atgctcccc	15540
acccccgcc	acagctctct	tgagacctgc	ctgattcttt	gtatgaccag	tgattttctt	15600
ttaaattaaa	aaccttgata	attttgtatt	ttaatgacc	tgttctgaat	atgtaattct	15660
tctaatacat	acatgattaa	gccatagctt	aaacatttct	ttctttcttt	ttctttcttc	15720
aagacaggg	ttctctgtat	agtccctctg	gctgtcctgg	aacttgatct	aaagaccagg	15780
ctagcctgga	actcagggat	ctgcctctct	ttgtcccaa	gtactaaaag	gcgtgcagta	15840
ccactcttg	ctttttgtgg	gggttttgag	tcaatttcat	gtggcctgga	tagtgtggct	15900
ccaaatccac	ttgtataat	aagatgactt	tgaactttgt	ttgttttgt	attttttgag	15960
acaggatatc	tctgtgaaat	tctgactgtc	ttggaactct	atctgtagac	cagactggcc	16020
ttgaactcag	agatctgect	gcctttgact	cctgaatgct	gctgggatta	aaggcataaa	16080
ccaccattcc	tgattttcct	ctttccagtc	tttcaagtgg	tggaatcaca	gatgtttgcc	16140
accaggttg	gcttgagcca	gactgccttc	ctgcctgect	tatttccttt	cttccttcct	16200
tcttttcata	tttaattgt	atgtatttac	ttgtgagcaa	gtgcatgtct	ggaggatat	16260
gcctacctat	gagtcagttc	tctctttcca	ccatgtgggt	gtgaaggatt	gaattaaggt	16320
catcagaatt	ggcagcaagg	ggttttgatg	acctctgggt	tgagtatttc	tttagccag	16380
catcatgaca	ttgattgtcg	agaatatgga	cgatattctt	ttacgacaga	aatgacatca	16440
gatgtaccat	cgctgggtcc	caccattgct	tctggaaacc	ctggacctgg	gattcaaggt	16500
ggaggagctg	ttgtacagag	ggctattaag	cgacgggtcag	ggtaagtttg	aatgtttatc	16560

-continued

atccgtgtgt	ttctcttgta	ccatcaactt	ttgagttagt	tgctgttggc	tcttgtttat	16620
tcttgaccac	acatctaatt	gattacttac	tatactgctg	tcacataact	aaaactaact	16680
cttagtccct	ggattattcc	ttatccaggc	tctctatttt	aagtaaat	ctttaatttt	16740
ttttgtataa	tttgaatata	aatatagctg	taaagaaaaa	aatgaggact	ggagagatgg	16800
ctcagtgggt	aagagcactg	aggctcctgag	ttcaattccc	agcaccacaca	tgggtggctca	16860
caaccatctg	taatagaatc	ggatgccctc	gtctgggtatg	tttgaagaca	gctacagtgt	16920
gctcatacat	aaataaatgt	atctttaaagg	aaagaaaagg	atgaaacggg	cacacctatt	16980
acttatcatc	cgacctcact	cacagtgcct	gtatgtcacg	tagggttttg	gcttttatta	17040
cttacatcgt	tttcacataa	aaatttctat	acagggttaa	aattgttttc	tagtatcttt	17100
attgataagc	ctgtttaaaa	aaaaaaaaaa	cgaagccaaa	ccaaacccaa	attttctgaa	17160
aggtaaaggg	actgtggcaa	agaagagttt	cactgttggg	aaaaacaaac	aaacaaaacc	17220
aaacccaaaa	aaaccccaaa	aatctgttgg	ctttccttaa	gctctggtct	gcattctcaa	17280
aatcattttg	ttaagcttat	ttctttttta	at ttattaat	actttctttg	acttgagtg	17340
cacagttcat	ttagtttcaa	aagtctttat	tgaagtacca	gatttgaatg	tgccattgaa	17400
gtatgattgc	tgtcttagtc	aggatttcta	ttcctgcaca	aacatcatga	ccaagaagca	17460
agttaggagg	gaaaggggtt	attcgggtta	cacttccatg	ctgctgttca	tcaccaaagg	17520
aagtcaggac	tggaaactca	acaggccatg	gagggatgtt	ctttactggc	ttgtttcccc	17580
tggcttgctc	agcctgctct	tctatagaac	ccaagactac	cagccctgag	atgggtccac	17640
ccacaagggg	cctttccccc	ttggctacta	attgagaaaa	tgccctacag	ctggatctca	17700
tggaggcatt	tctccaactg	aagctccttt	ctctgtgata	actccagctg	tgccaagtgt	17760
acacaaaact	agccagtaca	attgctaata	ggctctaaag	atagatagga	aaagttccta	17820
aagttctgat	ggtcgttata	tttatgtata	aatatacaag	acacagtatg	acaaaagtct	17880
gcaatacctg	aagttctagc	agtcagtagg	gctgagtcag	gatggagact	gagtccatcc	17940
tgagttacat	agtgatactc	ttatctcaaa	acaaagcgaa	aaacaaatta	attttaaaat	18000
attatttttt	aaatatatag	aaacactgct	tttggacggg	aaagattgag	aaaagttttt	18060
aaaagaagtt	tgttttaggg	cagtggttct	caactttctt	aatcctgtga	ccttttaata	18120
tagttctcca	tgttggtggg	actacaacca	taaagttatt	attattttta	tttttatttt	18180
tttggttttt	cgagacaggg	tttctatgta	tagtctggc	tatcctggaa	ctcattttgt	18240
agaccaggct	ggtctcgagc	tcagaaatcc	gctgcctct	gcctcccaag	tgccgggatt	18300
aaaggtgtgt	gccaccacgc	cgggttcat	aaaattat	tagttctact	taataactgt	18360
aatcttgcta	ctgttaataa	ctgtaatgta	ggatatcaga	tatgcaactt	ccaaaggggt	18420
cgttggtgact	cacaggttga	gaacagctgc	tttagggcct	gtgaggtagc	ttgttaaaag	18480
cctagttagt	tacctttaat	tgattoccag	aaccacaca	caagtagaag	gagaaaacta	18540
actctaccaa	attgccctct	gacctctaca	tgagtgtggg	acctatatgc	acacactact	18600
aaagcacaca	aaaatattaa	acttaaaaat	gaatgaatga	gcagcaacca	catgggtggct	18660
cccagccatt	tgtaatgtga	tatgggtgcc	tcttctggcc	tgtgacata	tttgcaagca	18720
gaacacttaa	agcagtcaac	actctcaatc	tctgactttt	ctccagccca	aagagtgcac	18780
gctactcttc	cagagaatct	gaattcaggg	cctagaaccc	atgtcagtga	ctcacatctg	18840

-continued

tgatctagtt	ttggggttct	gccacccctt	ttctgggtac	ctgtattcac	atgggcatat	18900
atccctatac	agacacatca	taaaataaaa	tcatttttaa	aatcataaaa	gatgctctct	18960
tcagtattaa	aaacacattt	caaatagtg	ttgctttttt	tgttttttaa	caaagtctgt	19020
ttaatttgat	tttattat	tgacatagct	ttcttgtaga	ctcagctggc	ctgcgttctt	19080
cctgggtcca	cttcccaagt	gcttggaac	aaaaacatgt	gaccaccaca	cctagtttca	19140
gacagtcctg	ctgtgtagcc	atgttggct	ggaattcagt	atgtacacaa	agctggcctc	19200
ccactcatga	ttctcctgcc	ttagcttcct	atgtcgcagg	actacagtca	agtgcacta	19260
catctgggtt	ttgtggcacg	tctttaaggc	cagcccttga	gagacaaagg	cagtgtgggt	19320
gggagggcag	cttggtgtac	atggagggtt	ctgggacagt	cagagctatg	tagagagatc	19380
ttgtctccaa	acccaaaccc	aacctcattc	tcactatta	tatatattaa	catgcattta	19440
tatgtttatt	tactcactct	gtgtttgtgt	aggttagaaa	acaagttgtg	ggaaatcttt	19500
ctttaccatt	tgggtcccag	ggatccaatt	tatgcctgta	ggcttgggtg	cagggttttt	19560
aatttgctga	gctgtctatc	tctctggcct	cttgctttat	agttgctggt	gtctgggctg	19620
aaaagctccc	tgagggtatt	ttttttcttt	taccacgggt	cccacactat	tttgtgtggc	19680
gtgtgatctt	gctttcttgc	ttcttctttt	gacaggatct	ggctatgtag	cttaagctgg	19740
ccttggaatt	atcatccttt	tgcctctact	tgatgaatac	tttgagctaa	aggtacgtgc	19800
caccaaggct	ggccacttag	cacagtgatt	tgaatatggt	atatatttta	tttttagact	19860
aaacaacttt	tgtgtcttct	ttcctctatg	taatattgct	ttgaaagatg	tttcagaaaa	19920
ctgacaaggc	ttagattaga	tcataaaaa	gaaaactaga	tctcagggat	ttctgtttt	19980
tcaggcaggg	tctcacgtag	ctcacccaa	ccttgaactc	agtggtatag	ccaagggtga	20040
ccttgagctc	ccgatcatcc	tgctgccacg	tcccttgtgg	cagaattcca	ggtgtgtagg	20100
tgtgtgccac	catgtccagt	tttacgtgt	actggaattg	aaccggggct	tctgactcc	20160
tcagctgagc	tgcattctta	gactctgggc	gctatttata	ctcgtatctc	ttcctgggtta	20220
tggtagctgc	ctcctgtatg	gaatccctgg	tggaggggga	gggggtcggt	gctgctgctg	20280
ctgetccctc	acttcttcat	tttgcttttt	gaaacagggt	ctgattatgt	agccaaggct	20340
agcttagaat	tcattatgtg	tctgaggata	gccttgaact	cccagaaccc	accacaggct	20400
ctggacgggt	ggttctatat	aggcacccgt	acggctgcct	tttactgcct	aacttctgcc	20460
cagtgtgaat	actatgaaaa	gcagtattta	tagacatggt	ttgtttttgc	ttctgtccac	20520
ttttccttcc	attaagggtga	gtacataggc	atcttttggt	aatatgtttt	gctttcttat	20580
ggtgttatct	ttactgtatt	atcatcaata	aacttagaat	attgtttggt	gcctttcccc	20640
aggctggatt	ttgatgatga	agtagaagtg	aacactaaat	ttttgaggta	agatttaaaa	20700
atatttttag	agacttctta	gtggggtgga	gggctgggtg	ctggctcagc	aggtaacagc	20760
actcctgcc	agcaggatgg	tctgagtttg	atacccaaag	ttactgctga	aggagagagc	20820
tgactgctgt	aaacagccct	ctgatctcca	catgctggct	gaggcgtgag	cacccatcac	20880
cctcacagat	aactaaatgt	catcagatta	ttttcagatc	accagctggg	aatgtagctt	20940
ggtgggatgc	ttgcctccta	tgcctcaggt	tcaatccata	gtaccaagaa	ggttatttaa	21000
gtatgtttat	actttgggca	ttgtcctaaa	gaatatgctt	catcctaaaa	ctatgttttc	21060
ctacatcata	ggatagtttc	aggcatttta	ttatttttag	agagaatact	tcagggagga	21120

-continued

gggcacagaa	aatataagcc	agtcattgtg	attcatggct	taagagaagt	aacacactag	21180
ggagattgct	cagtgggttaa	gaccttggcg	ttgcaaactc	aaggctaata	gttcagatca	21240
ccaaatctca	cataaattct	gagtgggcat	agcagcctgc	ttcctgtctt	ggaaggtaga	21300
gacaggagag	caagctggca	ttgagaataa	ttctatctgc	aacctgtgaa	tttgattgag	21360
aaatthttgtc	taattgaata	aagtagtaga	gtgatagagg	aggattcctg	acattaacct	21420
tggacctcta	cctgtatgtc	cactcacgtg	taatgcaccc	acacgtgtga	gtgctgagtt	21480
tgttattatt	ttgttcccat	ctgtcccatg	agccctgggt	gagattaaat	gaggtctgct	21540
catcaagtaa	ggtagaagag	agatgaaggg	ttatatcaac	tttgggcttc	ttcatacttg	21600
ttcaccacaca	cacatgagca	cccacacaga	cctgtgccta	taccatata	aacatgcgta	21660
tacatacaaaa	tggaaaaata	aaaaaaaaag	ttgattcgtt	ttcacaggtc	tataattgac	21720
taaatcttgc	ttgggttcat	ggtaagattg	tgctcagcca	cctggcttat	taaaagtatt	21780
actcaactgg	cacagtgtga	cctctgtctg	tctgtctgtc	tgtctgtcta	tctgtctctg	21840
tctgtctctc	tctctcttgc	tctctctctc	tcattgttctc	tctctctcac	acacacactt	21900
gcactctcac	ttaaactctt	tctccatctc	tccctcctta	tttctcttat	ccccattgtc	21960
ttgtcttcaa	acagaggagt	gtggtgatgg	ttgtaacaca	aagggcaagt	ctccgtgtgc	22020
ttacaagacc	cctgcttctg	tgtctttgtc	cttcaactgat	gtctcttagg	ccagagcgct	22080
tgtgtatccg	tgtcctgagt	cactgctgta	gagggctaca	gaaggacgta	gatgttagag	22140
ggaataattt	gataatgtc	tactctgtca	tgctgcagta	cctgttggcc	ccttttttag	22200
gtagcaggaa	ttagagggtc	tgtatgtata	aatggtgatg	gttgggcagg	gtctcatgta	22260
atccaggcct	gcctcaaaact	ttatatagcc	tgagatggga	tggcggcttg	aatgagaatg	22320
ctcacggtaa	ggttgtgtgt	ttgagtgtct	gctccccagt	tggtagacct	ttttttgaag	22380
ggttaggtgt	ggccttgggt	ggttgtgtgg	cccaagtggg	tgtctctagg	actacctgcg	22440
caggggaggt	agtgagatag	actttctctc	tcaatcaata	atcaaaataa	tattacactg	22500
gcttgcccac	aggccactct	gatagagaca	ttgtctcagt	tgggattccc	tcttctcaga	22560
tgctcagggt	tgtgtcaaat	tgatagaaac	gaaccagcac	agcaattaaa	cgtaattctt	22620
ctgatactta	gtggatccta	ataaatgtga	agaagaaaaa	agatttcact	ttttgcctta	22680
ggcaagcttt	cattgttact	gctggattta	tctattttta	tcttaagtgt	tttacctgta	22740
agtgtgtata	tcgtgtctgc	agaggccaga	agagggagtt	gggtctctta	gtactaggag	22800
ttatagatga	ttgtgagctg	ccatatgggt	gttggtgtta	tggagtatcc	accagaggat	22860
gcttggaat	ggatttaact	caatagaaag	ttactattag	cctgccagca	actacactgg	22920
tgtttgggat	tccaatgcag	cactcagcct	ttctcagggt	gagcttttaa	acacgacagt	22980
atgttctgtg	ttgttggcat	acttcagtta	acaagaacag	ttagccagaa	gcagaactgc	23040
agaagccaaa	gagactttcc	cagaactgca	gactttgatg	gattaggcct	ttgttttagt	23100
tttggtaggt	agtgctgtat	acatactgaa	tttcacaacc	tgaatgggtc	ttctatcaag	23160
ggatcaattg	tgttaaggtc	tggagctatg	ttagtactgt	gaactgaacc	caggctcctc	23220
gcaaaagcag	caactgttct	taataactga	gccatttttc	cacccttaag	atagcatttt	23280
cacacaggac	tattgggaat	gtcttcatta	gagaattctt	aattacagtc	acatgatgtt	23340
actggaccta	tgttgtatga	atgctacagg	ggtaactaga	gtattttgtc	ctgtcaata	23400

-continued

gttttgacct	tgagttatct	cacaaaatca	agtagtcata	agttttgtaa	catttttggt	23460
cttatcagac	tactatatga	ccgtgggttc	aaacaattat	aatgggagtt	ataaaagtct	23520
aattacatag	gacatagcta	ttataacttc	agagtgcata	gaattcatca	ttcatgtttg	23580
tgatgatatt	cacataataa	tggtgacatg	atgggtgtgc	tggtgtgatt	taaatgtagc	23640
acatatgtgt	acagttaata	acacttgagt	ataaaaaaat	cccttggtga	tgtatttact	23700
atgttacaat	gttcattcat	gtttgcactg	ttagtaatac	ggcacaggga	ttactgaatg	23760
ctggggaagc	actgtgccac	tgagtcagcc	ctggccctta	ttgtgttat	tttagagctg	23820
cccccttctt	actgaatgac	aaagtttact	ttacacatt	gtatcatgta	attgccagtt	23880
tgtgaaactt	acttaagtcc	taatagtctt	ttttgcttgt	cctgaagaag	taaaatgtag	23940
aattgggaaa	aaatacttgc	aatcatgga	tcttagcagc	agtcggtatc	tagaatatgt	24000
aataaactac	aattctgata	caacctttga	aaagtgtttt	aatatttaag	atgaagaact	24060
gtgggaattg	gagagatggc	tcagctatta	agagtgtctg	ctgctctttg	agagtactag	24120
agttttgtac	ctggaaccca	ctttaggcaa	cttacaactg	cctataacta	cagcgccaaa	24180
ggatctagtg	ccctcttctg	gcttcacacg	tctcccaaac	acatggcaaa	gcacacactc	24240
acaaatagaa	atagaaataa	atgtttatct	attttaagta	gaatttggtg	caacttaatt	24300
cagtgtctgt	ctagagtgc	tgaagctctg	gggtcccttc	ccagcactgc	ataagccagg	24360
catgggtggg	tacacagcct	tggggagact	taatcaggac	gattataggt	tcaagtttga	24420
ggtcaccctg	cactgtatag	ccagacctta	tctatacaag	attaaaaaaa	ccaaacaaaa	24480
caataatacc	cccagccaag	tatggtacct	gtaattccag	cactggggta	atggcagcag	24540
cttagtgagt	tctaccttaa	tcaagttaca	taggaaacag	tttcaaaaag	ataagacaga	24600
aatgacagca	gctgtgctct	tgatgctgca	cagtgggttaa	aatagggtta	cagtgtagct	24660
cagtgggtgaa	gcgtgtgctt	agcgtgtgca	cggcctgggc	ttcattccca	gcactactct	24720
gcgtgtgtgt	actaagaagg	aaattctgaa	ttttattcat	ccagttcagt	tagtgtccat	24780
ggatagacag	cgatagtaac	tgtataggca	tgcctttgtt	gctagtgtag	gggaagaaaag	24840
accttctctt	tcttctaagc	attttgatga	ccaagttgat	aagacaaact	gactggaggc	24900
aggtaaacag	aagaggtaga	tagactaata	tgtggtctaa	gagtagccta	gctgccccaa	24960
gggaaaaacag	taagtgtgca	gtcagtgaaa	ttggagaatt	tatatggtct	catagggaatg	25020
gcaacatagg	caactcagta	gaagattcac	agatacagtg	aatgggcatt	tgagtaaatgg	25080
gtgatagtgt	tgccacagtt	tgccttgatc	tatagtgtgc	tcttgacctc	ctgtcctttg	25140
gttagtgact	ctttccaggt	tgataaatct	tcctagaggg	tatttgggtg	tataagagaa	25200
cttaatgaat	gtgtgtgtgt	gtcattgtgt	gttttaaaaca	ttttgcgtgt	gtgtgtgtgt	25260
gtatcttgac	acatgtgcta	cacatgtatg	aaggtcagag	aaaacttgga	ggaataggta	25320
tccgcgccct	cccccttcac	cgcccccccc	ccctcccatg	taggttcttg	gaactcagat	25380
cagcaggctt	ggcagcaaat	gttttatcta	ttgaaacatc	tcaccactta	cctccatttt	25440
gtttgacaga	atccacttg	gtaatccaat	caagccttgt	atagcccagg	ctttacacaa	25500
atgtacggag	agcctctttt	ctcagaggct	actgtaggct	caagccacta	caccctgctt	25560
agcacttggt	tttgttttgt	tgtaaatagg	tctgactctg	tagctttggc	tggtctgaaa	25620
cttcacagag	tctgcctgtc	tctgccttct	aattctggga	ataaagtgtg	gacccctaac	25680

-continued

acagtattgt	tttttcacat	tctttcta	ctgaataatc	agtagactag	agcattgagg	25740
tattttctga	ctcctttgag	ttaaagtcta	tctcttcatg	tgtgcgcct	cttgtgggga	25800
ggacagtaat	cagctagaca	gatgagagca	cttcaatagg	acaggggtat	tcacactact	25860
gctgtgtaac	tgaggcccat	attagactga	agacctcaag	actttggggg	aggacacatt	25920
tcacctttag	gctgacgtgg	tgaaaaggaa	gtgaaatggg	atgttagcta	gagaggcttc	25980
ctagaaaagg	aaaggaagt	acaaagaccg	gaagcaagac	gggaagaatg	tagctgctgt	26040
tgggaacaca	gagtccttgc	ttgtaggcca	cagttaggag	ggaagtagga	atccccagaa	26100
ggcagtagcc	aggagcttta	ccatcttgga	gaacctttct	cagaggaaga	gttagggagt	26160
agtcttgttt	caatttaaatg	cttttgtttg	tttgttttac	accaaacata	gattactttc	26220
aaagttggta	aaagcaaatt	taaaaatgaa	aggggggaaa	atgccaaaag	acatggagag	26280
gcattttctc	aaagaaaaga	tacaaatggc	caagaagcat	gtgaaagggt	gacattagta	26340
atcattcaga	gatatttagg	aggtatacaa	gtcaaagata	acatttatat	ccaatccaga	26400
gaccactatc	aaaacccaaa	caaaatcgga	gctaagtctg	gagactgata	cccaccagcc	26460
tcccatgggt	agagggaaac	cagggtcgca	caggagctc	ctgtctcaaa	aagacacaag	26520
taacccccca	gaaaataaca	aaattgctag	agaagtggag	gaatcggaac	agttatacac	26580
tgtgatattg	taaaatggta	cagtcacaat	ggaagagaat	atggtgccac	tttacaagtt	26640
acagctcagg	gtcacttgcc	tcacaagctt	aaaagattcg	attgctcata	ctaaaacttt	26700
gtatattagc	ttttttctga	agactttaga	aatttttatt	tttatatgtg	tgttttgcct	26760
acatatgtat	cttgcacagt	atgtgtgcct	ggttcctaga	cctggagtta	cagacaattg	26820
taagctgcca	ggtgggttct	gagaactgaa	catgggctct	ctgcatgaac	aacaagtgtc	26880
tgtaatcatt	gagctctctc	tctagccct	aatgaatta	gttttgagct	aggtatgatg	26940
gcacatacat	ataatcccaa	cacttgaggc	ttatgtaaaa	ggatcgctgt	gaattcaagt	27000
ctgagctgct	ctcaataatt	acacacagag	acctaacgca	tagagtgtct	ttgagggtgac	27060
tgatctcgga	acccacactg	tgaaaggata	gagttgttct	tgaaagtgtg	tctccacctc	27120
catatctgcc	ctgtggctgc	aaacacaagt	ttggttttga	tggcctgaaa	cttgcctgtc	27180
agaccatgcc	gacctccaac	ttgaactgat	cctctttgaa	cttgcatctc	gcatgcaggg	27240
gttcagttgt	gcacaattta	tattttcata	catatatata	aggcattgta	tacccacccc	27300
ctcacctcgg	gacatcctct	tctcgatagt	ccccttcctt	ttcccaacta	gttctctctc	27360
tactttcgtg	accttttttt	ttttttcttt	ttcttttggg	gtgggatgtt	tcattagggg	27420
tgcttaccag	tagtatgtgt	gagtgattac	actttcctcg	gggctacaac	aatgaagaaa	27480
agctctccca	gcaactaact	gcttatagat	cctcaagggg	gtttgtggct	ttgtgaactc	27540
ctccccctt	ctatgctagg	atgttgtgta	gtttttgtag	tcacagctgt	tgtgaattca	27600
agtatgcatt	gctcatgtca	tttcagaagg	cagtgttcca	caacagtctg	ccctttctct	27660
taactcagag	tgtaactct	tatgcaatgg	tcctgacccc	ttggaggctt	tggtatctct	27720
tttcccatcc	cccatcctt	gtggagtgtt	gctgtgttgc	tcagaccagc	ctcctacacc	27780
tggctcaaat	gttcttttct	ctcagctgcc	taagtagggc	taaagaactg	caggcacatg	27840
ctaccacacc	cagcttaaa	caggggtcaaa	atatgggtat	tagatgaata	cccatattta	27900
tgatcctgtt	tttcacagaa	gaatgaaaac	atgaaaaata	taccacacag	ctgttctatt	27960

-continued

ggttttttga	tttttgtttt	tgtttttgtt	tttttaaagc	tacaattaaa	aaacaaacaa	28020
actgagtcag	gcttagtgat	tgacacctgt	aataagcaat	tgggaggcag	aggcaaaggg	28080
tctgtaagtt	gagagtgaat	gccagactag	ccagtgtctac	atagctgtcc	ccatctcaaa	28140
aaaaaccccc	ccccccggaa	aaaaacaaaa	caaaaacccc	aaatatattc	ccaacttttag	28200
agaaatcaca	agacatttca	tgttttcatc	ataccatctt	tctgtgtgtg	gtcactgaga	28260
catgatagtc	atcggtcttc	agtgttctct	cagatgctat	tagtgtctgc	tgctttgtgg	28320
tgctgggtcca	ttatctttcc	ctggttgagta	gttttattta	tttctagttt	ttatttcaga	28380
gcggagtaga	tataagtaca	agggtttgaa	ttaatccctg	ccctttcttt	tcagatgcga	28440
tgatgaccag	atgtgtaatg	acaaagagcg	gtttgccagg	taatgtacta	gaattcttgt	28500
cctggttatg	ggatcaagca	gtctaaatgt	tggatttaaa	ttttatctag	gtgagagtga	28560
atttctctgg	ttagtctcct	cctcttctga	agtttgaaac	agcctggaat	ttatgcatgc	28620
tcattgactt	gaagctaggt	atatttaaca	taatgtttct	ctcatgcatg	caagtttttag	28680
taatgtgtat	attgcatcta	caggatcaca	aactgtagac	ttcttgggca	tattatatatt	28740
gtacaaatac	agaagaatct	tttatagaaa	atggtttatt	catttaaatg	agtttttatt	28800
ctggatacca	aacttaaaatt	tgtttaagta	actgtcagaa	gattatgaaa	tatactgatt	28860
ttactttttt	tttctctctc	cacccctgat	tttacttttt	attaaagagt	aatcattctc	28920
aactcatata	ctggttttac	ttttagaaaa	ttcttgctgt	aagttaactct	tttaaaaaga	28980
ggggagggtg	tcatggggct	ggagagatgg	ctctatgggt	aaaagtgcct	gttgctctga	29040
cagaggacct	gaatttgggt	tctagcatgc	acaaccaggg	agtctgacat	cctcttttgg	29100
cttctgttga	cgtctacatg	tacatgatca	tacatatata	tagatgtaca	cgtatacaca	29160
tacatacatg	catgcataca	tacatacata	catacataca	tgctttattt	attatcatta	29220
agtggtcatg	cttacttggg	gagccaagat	gttgggttcc	aagtataagc	ctgtgtccct	29280
gaccactctc	cccagtatct	tcaccccagc	tgagtatctc	tggagagaga	cccagaaggc	29340
acaagtagaa	ggtttgggca	taagggtgaa	gctcagcggg	agtacttgct	tcagtacagt	29400
ggccccaac	accaaagca	caataaagac	cctgccttga	ttcattgaac	ttattcagga	29460
tcaacaaatg	tttaatctaa	tttcagaacc	actcccaaga	atttactcat	tttttaggag	29520
ctctgctggt	atttgggccc	ctcatcttct	ggtattatgt	tttcaaaaca	gatagggaca	29580
gaaaatatag	gaaaattgaa	ctgaacattt	aacctctcat	ttaatttggc	aagggacttt	29640
tattgctata	taaatagatc	tactaattta	aactctggaa	ataaataagt	aaataaatca	29700
atactttaag	ctcaaatcct	gaaagttttt	cccttacaca	cacacacaca	cacacacaca	29760
cacacacaca	cacacacaca	cacatatata	cagtgggtact	catgtgcctg	tacttatata	29820
tatacatgtg	atagacacac	ttaatgataa	taaataatta	aaaatttaga	agatactgaa	29880
tttttggctg	gggagatgac	tcaggattta	aagtgcctaa	cccagaacc	cacataaaat	29940
cttgatacag	agtatcccaa	gtctatgatc	ctagtgagtc	tttattgggc	gatagaagac	30000
agagatggga	atagccacaa	actcatggct	cagctaactt	ggtgtgtgca	gcagtgaaca	30060
ataagagtga	ctctgggctg	gagagatggc	gcagtgggtga	agactgctct	tctagaggtc	30120
ctgagttcaa	ttaccagcga	ccacatgggtg	gtccacaacc	atctgaaatg	ggatctgatg	30180
ccctcttctg	gtgtgtctga	agacagctat	agtacagttg	tatacataaa	ataaatattt	30240

-continued

tttaaaaaac	ttaaaaaaa	agagtgtctg	tctcagacta	agtggaaggc	atcgaacaac	30300
atctgaggct	gccttttaac	ttcccttgc	atttcattgca	cacgcattgca	cgtgcacgca	30360
cacacataaa	attgagtttg	tgatcctctc	aaaaattagt	aactttatgt	ttaaatttgt	30420
atgtaattga	ttactttaaa	aatgatctat	ttcattttta	attatgtgtt	tgtatagatt	30480
atacagtttt	tatagataaa	tggttatata	catatgaatt	tggataccaa	agaagacat	30540
caggctccta	gaaacgcagc	aagcccat	acccaccaag	ctgatcctat	agcccaatga	30600
atacttactt	aaggtttgat	tacattgatt	gattgattga	gaaagtatgt	gtgtttgtga	30660
catgccaa	tgctaagctc	agaggacaac	ttctaggagc	agattcctgc	ctttcacccg	30720
tgagtcctag	tgttgaaact	cagatttagc	agcaagcacc	tttacctatt	aagcctgtct	30780
gctatgtctt	ctgtgagtac	tgatcaacag	tgtttactca	ttgctcagct	gtctgaatgg	30840
gatctacttt	gaggaccact	gatcgagaga	accaagaaat	atcaggaaga	atagttaact	30900
cttagacaca	gtgttggcag	tatatagagt	tgactgaaaa	gagcaggtag	gtaggtaggt	30960
agtaggtaag	taataggtag	aaagaggag	ggtagataga	atctgctgaa	gtattaggt	31020
agctatgaaa	tcatgagtac	ttgggccag	aaatgttgcc	gtgacactag	tgaagaatg	31080
aatatagggt	gttttccaag	agcagtgtat	caaaacttct	tgaataaat	gaaatctaaa	31140
ggatacagta	atctttaaag	tgaaggttaa	ttattgattt	tgggtaataa	tctttcacat	31200
tctattaaaa	agtctagcta	taaaactgga	ggtagatcctg	taacacttgt	aatggagggtg	31260
gaggtaagag	attagaaatt	ctaggttagg	gactagagag	atggctcagt	agttaagagc	31320
actggctact	ccctgtagt	gacctgagtt	tgattcccag	cacttactgg	tggcgacaaa	31380
ccatgtatga	ttcagttctt	gggggagggt	ggggagtcca	atgccgcctt	catacatata	31440
tacatacata	catacatata	tacatacata	catacatata	tacagtaaaa	atacttacac	31500
acctaaaaat	aaaaataggt	aaatctttat	ttttttaggt	tactgggcag	cagggcagtg	31560
gtggcacatg	actttaatcc	cagcacttag	gaggcagagg	caggcaggat	agccagcctg	31620
ttctatagag	tgaattccag	gacagccagg	actagagaga	gaaactgttt	tgaaaaacag	31680
aacaaaagaa	aagttatttg	gctatgtagt	tcaagaccag	cgttggttc	atgtgacct	31740
aaaaaccaa	ggtcagatca	tcattagggc	agctaataca	ggccagtc	tcagtctttg	31800
atcgacactc	tggaaagcca	taaaacacaa	cctggagtat	ctaactcgcc	tatgtcctat	31860
tctgtttaga	aatattggag	tagagagggg	gttgtgtgac	tctactatta	attttaagg	31920
aattaattaa	aggaatttta	aatgattaac	ctcaaacaaa	aatgcatttc	ttagagttac	31980
agtttgttat	gatagtttac	ctcatacacc	accagaaatt	cagtaggtga	aaagctaaaa	32040
ataggtgaat	ttacttatct	tttgaaaatg	aatgttttgt	tgcttgtaa	aaactatcta	32100
ggataaggaa	caggcagggtg	tgactactct	gttatctgtc	ttctctcag	catgtgtgca	32160
tacattttat	agtattcatg	actatctgca	gttctaactt	ttttatttc	ttatttttaa	32220
cattcaacaa	ttttattcca	gtttaaaaga	agaacagaa	aggtaagctg	taaaatgtca	32280
gccagtggct	ggaggaagag	agtggaggaa	agaggaagca	aggccacgcc	attttaagct	32340
ggcgtggaga	tgagacattt	gaggggcgct	ttagggaaag	agtagggaag	cccaaacgc	32400
tggtgagacg	catgcttgga	aaagacacag	agagttgttt	tgggtgatca	aatgacctc	32460
tcacaggggt	ctcatatcag	acatcctgca	tatcagatgt	ttatattaca	aaaataattt	32520

-continued

atgattgggg	tcaccacagc	atgagggctg	ataaagggtt	gcagcattag	gaaggctgag	32580
aagaaccact	gtgctagaga	aaggagaaa	gagaagggtga	cagataatga	tccttacatg	32640
gctgaggcct	gttcagggtc	tgctattaga	cattagctga	ttgtgtttat	gtatgtgagt	32700
atgtgcatat	gaaggcatat	aggattttcc	agttgaattt	acaggcagct	gtaagctatc	32760
cagcatggat	gctggggatc	agactccgat	cctgtgccag	aacagtgtgt	gcttttaact	32820
cctgagccat	ctttccttct	cctttttttg	agttaagatc	tcaccaggcc	aggctttcct	32880
ggaacctgca	gaaaataatt	ttacctttgt	ttctgactgt	tggtattaaa	taaagttgag	32940
caccaccaca	gccagttggt	ctttttctac	tgatcatttg	tgtatatatg	tgcatggaga	33000
ggacagagga	caactccagg	tgtcatttct	cagccccacc	cccacccccg	ccgagatgga	33060
gcccttctct	gtcttggtt	gcactaggtc	gactaggatg	ctgttcagtg	agcccatagg	33120
atcctcctat	ctctgccttt	cctgtgccaa	gattgtaagg	attgtagtgt	ccactttatt	33180
tttacaata	ttgataaaat	tattattatt	aagctcaagt	tttactctgt	tgcaaatccc	33240
taggtcaag	cagttcttcc	atttcacatc	caccagtagc	taggactaca	aggtccctgc	33300
ttcctgctgt	atccatttta	aggcagagtc	ttaggaagtt	attttatttg	cgtgtctggc	33360
tttattattt	tggtttatgt	gagacagtct	tggcctgtca	cccatgctca	tgctctcagg	33420
ggatgattga	gattatgctc	catggaggac	aggagagggc	gtcaggctct	ctagagttag	33480
agctagagac	tgcatgaat	tgctggacat	tgaaccagtc	ttctctggag	gagtagccag	33540
tgttccttat	ctactcacct	catctctcca	gccccatcat	ctttaatagt	gaagtctttt	33600
tggtactatta	atatacctta	ctagataatt	tatttgaggc	ttatctctct	taaaatgagc	33660
acttataata	ctgaggttagc	tagtaccttg	ttttggtttg	tttgcgtttt	tgtgtagcct	33720
ggctgtcctg	gaactcactt	tgtagaccag	gctggcctca	agctcagaaa	tcacactgcc	33780
tctgcctccc	aagtgtctgg	attaaaggcg	tgcgccacca	caccagcccc	ttgttttttt	33840
tcagttgctt	ctctctcccc	tttttgtgcg	gtgggtattg	agccagtcct	tcacatttgc	33900
cctggttatc	ctggaactct	ctatctctgt	gtgtaccaat	ctggacttga	actcctcaag	33960
tgctaggatc	ggaggcacca	ccaccatgcc	tagccctctc	caccattctc	taaagtgttt	34020
tgtttttctg	gaagagttta	atgaaaacct	ttgtctttct	tcgagggagg	agggattgac	34080
atactgggta	aacctagaaa	gaaatgctaa	ggcgctctaa	ccagagttca	ttaaattagg	34140
agtggtgtag	tgatagagaa	tatgcaggaa	acctagctct	tgatttttat	catgtgatca	34200
tgcaagcta	cacggctcgg	tgtatggctt	tcactccaag	cctgagaact	caggttcttc	34260
ctcacagggt	agaaggagag	agccaactcc	cgcagtcgcc	ttctgacctg	tggcacacag	34320
acacactaag	tactacaatg	ggaaaaataa	atcttgtcat	aatttgtgtg	tgtgaatgtg	34380
tgtgtgtgag	gaaattatat	ttctaaccg	ttgtttgaag	ctgtgtaatc	tagtcactag	34440
tagacaatat	cgaatgtgaa	taagtgttct	ttcccagatt	ggcagcagtt	tataagaatg	34500
ataattctga	taattctgaa	tttcttggtt	ggttcttggt	cacactctgt	atcttttggt	34560
tctgtagaga	ttgtttgaca	aagtgttttt	tgtgttgaga	ttatgttagt	ttctaattgt	34620
ccttgacttt	cgacttataa	tttacttggt	acaaaaatac	agttctatag	gttctcaagg	34680
ttcttccttg	tatggccttt	cctcactttt	tctgtatcca	tttcatctct	tcctttcttt	34740
ccttttcatt	ttgcatttca	ttttccctcc	ctcgttttca	tctgcctttt	cttctttcct	34800

-continued

ttcttccttt	ttattttaat	tttcgcttag	ttcatcaatt	ctgttttttag	gtcggatgat	34860
gagcagagct	ctgcggataa	agagagactt	gccaggtagg	agctgtgctg	tttagcatga	34920
agcacatact	gccttcttac	cctttgtcta	acccatcttt	ttttcccttt	ctgtattttt	34980
ctcttacctg	tggcaaagga	ggacatgagg	ttttacaagt	tggggtacaa	taagaacttt	35040
ggcttcccca	acaggaagtg	ggtgaattaa	gccaggtagt	gtggctcact	cttttgatcc	35100
ctgcatttgg	gaagcagagt	ggagtctctg	aagattgagg	ccagcctggg	ttacaaagaa	35160
attctaagac	agagaaaccc	tacctgaggg	tgatggaaga	ataaattata	aattactgtt	35220
catctttaag	atttttattt	tttctttact	tcactactaa	gttccacaga	taatgattta	35280
gaagtaatgt	ggctgtgtcc	acagatgctt	taacaggcgc	atactctctc	agaataccga	35340
taattaccat	agttctatca	gaataccgat	aattaccata	gctcccagaa	tttaggccat	35400
agcacatact	ctgacttccc	tatgcgatt	cacagtctag	attactatga	tggtagaact	35460
gattgaatcc	ttataatttc	tgaggaaagt	tttagctact	ttggtatgac	tatttaaagg	35520
atggattttc	taggggtggag	agatagtctg	taaaataact	gctctgcagg	tatgattacc	35580
agagtttgat	cctcagaacc	cattgaatag	aagggtgcgg	gtttataact	gcacatgttt	35640
atgattctag	tacaataggg	aagcaggggc	agacctctca	ctgggcagct	gcactggcct	35700
aggagaagag	ccctgggtcc	ccatgagaga	tgctgtctca	gaaaacaacg	tgggaagtgg	35760
atatcttaaa	aatgacattt	taaattgacc	tttggatttg	acatacatgc	acatgcatgc	35820
tcacacagtg	tgtatttgca	cacatagttt	tctggacttc	agtctcagaa	atttgtcaga	35880
tactaagaag	atgggtactt	caaaattaag	agtagatttt	tttaaattgc	tgagagtagc	35940
taaatattaa	cctataaagt	aggttctttt	ttctttcgga	aagagaccac	ttttcctttc	36000
cttcaggaca	gggtctcatg	tactttatgc	aggccctaac	gtcctgatcc	tctgcccggg	36060
gtgctggatt	gcaaggggtg	gccgtcatgt	ccagataaac	atctccatag	gcagatttcc	36120
ttctgagggg	ctcccagctt	tgtgtgttgt	gggtgacact	gtgacactca	ctgagctaca	36180
ttcagggacc	tgttttagtt	ctcttttagag	tgtgttccat	gatacagaaa	tagtgctttc	36240
ctgctctggc	ctttgagttg	gtgtacctgg	atcattataa	aaatactttt	accactgtcc	36300
ccttggtgta	cttcttcaag	ctaggccaca	cattcattct	gtgactgtta	accaggggtt	36360
gctactgcga	tgtttccagc	cttcagagaa	ctggaaggcc	ttacactggg	gaggagggca	36420
gctctgagaa	agccagctaa	ctcttgcttc	atttggtctc	ttaaacaaca	ggatgtcagt	36480
gttaggggtt	gtggttttgt	ttttctcttc	agaagagatc	cataagtggc	gagagagata	36540
cataaagaca	gtaaagccaa	gctgttcctt	cgaggcgtcc	tcgtgggaga	ccccaagag	36600
tccatttgta	aactcttagg	ttattctctt	tgacagttgt	attgcaatcc	tgctctcagt	36660
ttgcggtctt	tgttaccctg	gtgagatgcg	ggttctcttt	cagtgtcttt	gatgttcatt	36720
tcccagctca	ctctctcttc	cacaatacct	tttggccagg	ctgggaaacc	acatgataac	36780
cagcactctt	ttaagttcag	cgcactgcc	aaccagaga	agaattttgt	gcattagtat	36840
aacaaataaa	attccaacat	acccaattc	tgtatcttaa	tgccataagc	aactttgaca	36900
aggcagcatt	taataacta	aaagaattta	cactatcatg	tcttcttttt	ctttcctttt	36960
ttcttttttg	gataagatct	cactatgtag	cgctggctgt	tctagaactc	agagattccc	37020
ctgcctccac	ctctgagtac	tgcaattaaa	ggtaggggcc	accacctggg	cgcgcgctcg	37080

-continued

ctctctctct ctctctctct ctctctctct ctctctctct ctctctctct cacacacaca	37140
cacacacaca cacacacaca cacgctctcc attttaagg cagtcttatg tattccagga	37200
gggtgagaagg aattatccac tcaagtgtg gactcacagg ttctcctgac tgctagcgat	37260
cagaccacaga gccttgccct tgctagacaa gcaactccaac acctgagcta aattaccagg	37320
ccaaggtggc tgctgctttt cttcttcctt aaaaaggagg cattgggtag ttttgagatc	37380
catcttgctt catagcccag gctggcttca aactcacctt gaagtgtatg gtgattctct	37440
tgctcagcc tcccagtagc agggattata gacaggcatg tgccagcatg cctggcctca	37500
tttgatatt tggaacagg tatcactatg tagtccatgc tgccctgtat agcccaggct	37560
ggcctcaaac ccaaaactct tgtgctttat agtcttcgga gtgctgaatt gtagtatttg	37620
ctaccagctc tggcctttat actattattt ctttcataag ctactggttc atttacttaa	37680
cttttcaaaa gttggtcatt ttattttata gccttcaaat gttttaacta gaaaacatgt	37740
ggtcagtgaa gctgagattt atccccttag gaacttaaat gagtgaatc aacatttaa	37800
aaaacactca ctctcaacct tacccttag acaggatttc tgtgtgttgc ccttgcgtgt	37860
actttgtaga ccaggctggc ttagaactca gtgatccatc tgctgcctc tgctcatga	37920
gtgctgggat taaaggcatg caccaccaac acctgtttt aattatttct taaactattc	37980
actctgaagt ggtgatttaa tggaagtggc tgactggaga ggcgatatgt actgttctt	38040
tgctagact ttgttagttt gtttcattct tactctgat gaggttgcc tgettggtt	38100
ctgagatttg aacatcatca gacctaatg actgcatcct tcagcagctg accaggatc	38160
catatcactc tcctgatacc aaaggaacag atgtgaccac ctagaatgga gcctctttct	38220
ctttttttat gcagggaaaa tcatagttaa atagaacggc ggcgacgga caagatgaca	38280
gcttacatca cagaactgtc agacatgta cctacatgta gtgccctggc tcgaaaacca	38340
gacaagctaa ccatcttacg catggccgtt tctcacatga agtccttgag gggaactggc	38400
aacacatcta ctgatggctc ctacaagcca tcttcctca ctgatcaggc ccttgatct	38460
taaaactgac tctgggtata tctgtgaaa gttttggact aatttaattg tttgttttg	38520
ttgttgcctt ggtttttttt gggagggctt catgtagccc aggcgtgacat ccaactcagt	38580
atattgccaa catgtgccac catgtccagc ttcaggagag tgattcttca ggagacatca	38640
gatgtagaaa agtgaattca gcccttagct ataagtgatc aagtattggg ggagtgagaa	38700
tagataaatt tagttgtgag aacttattta gcaagggtgc aggtatttta gaacttggt	38760
catacaaatg acctgtgaag tgaaagaagg gtgtgtcccc agagagggtg ccacactcat	38820
ggatcagtg tccctgggtt atatttctag agcatggaag aaatctgcct cacccttgaa	38880
gcaactttta gtcttaacga tgagagacgt gtagtaacaa acccctgttg ctccatgata	38940
tgttttgtta cacttgatat atcatgagga aaacagaaag ggcagaaata cttgccatca	39000
ttcaggagcc ccatctaaga gttatctcac tattgccagg agagagaact aaatgtgagt	39060
agagtaaagc ggtgagtagt aagatgccta agtgaaaaac gatgggaaga ggcattcgga	39120
aaagagccgg tgcctttgtt aatagtttgt gtgtgataga tatacaatgg tggcatgtct	39180
aactttattt agtctctcta gacttgactg agaagtacta ggaaagacaa gttacatttc	39240
acttaaaat ccacgattgg gtagggcata gtggtgaatg cctttaatcc cagtactcag	39300
gaagctaagg ccagcttggt ctacagaggc ccaggccagc cagagctaca tagcaagacc	39360

-continued

ctgtttcaaa	aataaaaaga	catatgattg	ttcatacctt	gcctatgcaa	agccctgaat	39420
ttggtcccaa	cactatatgc	agttgtgtat	ggtaactgga	tatggctgct	cataaccctg	39480
ctttcagcac	tgaggcacia	gtaggagggt	gaggggttaga	gttattctca	aggccagcct	39540
gttaacatag	gagactgtct	aaaatagata	catacacaca	taagatgggc	atataggaga	39600
ctgtctaaaa	tagatacata	cacacataag	atggtcatat	aggagactgt	ctaaaataga	39660
tacatacaca	cataagatgg	taatatagga	gactgtctaa	aatagataga	cacataagat	39720
ggtaatatag	gagactgtct	aaaatagata	aatacacaca	taagatggta	acataggaga	39780
ctgtctaaaa	tagatacata	cacacataag	atggtaacat	aggagactgt	ctaaaataga	39840
tacatacaca	cataagatgg	taatatagga	gactgtctaa	aatagataga	tacacacata	39900
agatggtaat	ataggagact	gtctaaaata	gatacacaca	taagatggta	atataggaga	39960
ctgtctaaaa	tagatacata	cacacataag	atggtcatat	aggagactgt	ctaaaataga	40020
tacatacaca	cataagatgg	tcatatagga	gactgtctaa	aatagataga	tacacacata	40080
agatggtaat	ataggagact	gtctaaaata	gatacacaca	cacataagat	ggtaatatag	40140
gagactgtct	aaaatagata	catacacaca	taagatgggc	atataggaga	ctgtctaaaa	40200
tagatacata	cacacataag	atggtaatat	aggagactgt	ctaaaataga	tacacacata	40260
agatggtaat	ataggagact	gtctaaaata	gataaataca	cacataagat	ggtaacatag	40320
gagactgtct	aaaatagata	catacacaca	taagatggta	acataggaga	ctgtctaaaa	40380
tagatacata	cacacataag	atggtaatat	aggagactgt	ctaaaataga	tacatacaca	40440
cataagatgg	taatatagga	gactgtctaa	aatagataga	cacataagat	ggtaatatag	40500
gagactgtct	aaaatagata	catacacaca	taagatggta	atataggaga	ctgtctaaaa	40560
tagatacata	cacacataag	atggtcatat	aggagactgt	ctaaaataga	tacatacaca	40620
cataagatgg	tcatatagga	gactgtctaa	aatagataga	tacacacata	agatggtaat	40680
ataggagact	gtctaaaata	gatacacaca	cacataagat	ggtaatatag	gagactgtct	40740
aaaatagata	catacacaca	taagatggta	acataggaga	ctgtctaaaa	tagatacata	40800
cacacataag	atggtaacat	aggagactgt	ctaaaataga	tacatacaca	tataagatgg	40860
taatatagga	gactgtctaa	aatagataga	tacacatata	agatggtaat	ataggagact	40920
gtctaaagta	agtgtcaaca	tataaaatgt	gtgagtagtg	tgggaagttt	tagaaaatac	40980
aggaaatgac	acttaatgta	atgtcaccat	tgtgtgtctga	gaattatagg	aatacttctt	41040
gagagaaagg	gataaatgtt	ccaaataggg	cagtctgttt	gctagccatg	gagtacattt	41100
aatagctatg	tacatagaaa	tagtcaattc	atgtcctcag	aatacgtcag	gtatttatta	41160
aactccagtc	atgtcctctt	tgtggcaaac	caggtacttg	cgctatgaga	aatccaaaga	41220
atttaaaaag	gaaataaagg	tcactgggtg	aatcagataa	tataaattga	taactaataa	41280
tacgaaacta	gagttgtaac	aggaacagta	acaaggctaa	tagagtatag	gtatagaaga	41340
ggaactaggt	gctggccatg	gtgaccact	actgtagtcc	cagcagtcac	ggatatctgag	41400
ttacattgca	attcagtgat	acgtggaagt	gggggaggag	tgtgggtgta	tggagggtta	41460
gtacagggtg	tacttggtat	ttattttatg	atgtggaagc	atgtgtatgg	tttctaagaa	41520
gagaggatga	ataggatcta	ggaagtgttt	acatgtaaca	tacgaacaaa	gggaagagta	41580
tctgggcaga	aaataaagca	gaaatgaatg	gaatttcaga	agataactaag	caaaaatgaa	41640

-continued

atttctaggg	ttccatgggc	agtattaaca	ggttgtgtag	agagattgaa	tttaaaaaat	41700
gatgagaatc	caggagaagg	gacttgaatc	atcaattagg	aggatgtaat	tgaatcctca	41760
attacagaag	tagtgggtta	cagtgaagat	ggagggataa	ttgaaaagca	agagagtgtg	41820
aaatatgggc	tcacccatct	taccatcttt	tatctaccct	caaaatgaca	gtgatcta	41880
taggtttttg	tagtctgtac	ttagttaaac	ctttggctcc	tggtgagcat	ccgctcaaga	41940
gctctctgga	tttgtggatg	aaagacgtgt	gccagcttaa	ttttgatatg	ccttgactag	42000
ttcaatggct	gggcagtttc	aaaactccca	aagccagcaa	acactcccct	tgggtattcc	42060
tgggttaata	tcttttaaaa	tctgtatttt	ctttgcttcc	ctggctcctt	tggggcagcc	42120
ctttcttttt	ccccctttgt	tttccccag	ggaacctaga	agtcctgcct	ctttcatcct	42180
gcccacctgt	gctctttatt	gatcaatcaa	aaaccagttt	gggtgaccaa	aattagcatt	42240
ataacacaag	cagcattaga	ccaaaccac	ttcatgtttt	tatggttact	tcctaagcat	42300
taaaacctag	atcctttaat	aacatattct	gaacaagttg	agggaggcta	tgtttgtgtt	42360
tataagttgg	agtggaagg	gggaaagtga	gaggctccta	accctaacc	ctgccccctc	42420
cagaagtctt	atcattta	gtaagccttt	ttattttcct	ttgagtgtga	agaggcaa	42480
agcaacttag	agaaattgca	ggaatactta	ctgtaaaaag	tttgccagtg	gatatttagg	42540
gtaggaaccc	atggcttata	tcgtgggtata	agcctgtgat	tcctagtgtg	gcagtgcata	42600
tgtacccaag	gatcttgcgt	cttcccatga	tcagtgtgtg	atgttttttc	agagtteact	42660
attaactttg	gtttattttc	ttgaccagga	actgaaacat	ttgatcttgg	aggcagcaga	42720
tggctttctg	tttattgtct	cctgtgagac	tggacgggtg	gtgtatgtct	ctgactcagt	42780
gactcccgtt	ttgaaccagc	cacagtctga	atgggttcggg	agcacactgt	atgatcaggt	42840
gcacccagat	gatgtggata	aacttcgaga	gcagctctct	acatcagaaa	atgcccta	42900
aggtgagagc	tggctggaca	gcagatatgt	gggggaaaag	tctttatttc	actcaagtag	42960
ttaagatatt	taagcccgaa	aaacccaaaa	aaaaaaaaaa	aaaaaaaga	tatttaagcc	43020
tgtacattgg	ttggttgaat	ctagcaaaagc	ttctaaaatt	tttttcctta	atgactataa	43080
ttgtttttta	ttcacgtgca	aaatatccac	tctgtagctt	attcttagaa	aatatttcat	43140
cagtgcctgt	gttcttataa	aagctcattt	ctatctta	aatatcttaa	aataggatgg	43200
agaggctgtt	ggtagtgta	taagggactt	gtttgtgtgc	actgtatctc	tattaggtca	43260
tttccccctc	accagtaggt	gagactcagt	cctttaccat	cgtttgaga	ataagtgcc	43320
cctgttctca	gcaactgtac	aggaagtaac	aaaatggaaa	caaataacta	ggagttaaaa	43380
taggagaaac	tagggctgga	gagggtggctt	agtgggttaag	agcactgact	gctttttcag	43440
aggtcttgag	ttcaattctc	agcatggtga	gatgggtggc	cacaaccatc	tgtaatgaga	43500
tctgatgcct	tcctctgggtg	tgtctgaaga	tactacaatg	tactcataaa	catgaaataa	43560
ataaataagt	ctaaaaaatt	taaaagaaaa	agaaactcca	atatctttgc	agtgggaatg	43620
ttcatattaa	tgttgtttgt	ttgtttgttt	gtttgttttc	cccctctttt	gtgattttgt	43680
acatttcatt	tctataat	tccttttccc	caaatgttac	ttacattttt	aaaaaaataa	43740
ataaaggaga	gagactgttt	tgttttttga	cacatgcatg	tttcttagca	tgtaaaatta	43800
cttgttttta	aaccagacac	tgtccctacc	cgaagcgtga	cgatagttag	tgaactgcct	43860
aatggctcgg	tgggtgaagga	gcatgccacg	taagccacgc	agtcctacgc	cagtctgcag	43920

-continued

actgcataac	agtggaagca	gtgacagctc	cacatagttg	tcttctgacc	tcacataca	43980
ggagtgggct	cacatgcaca	atagttctag	tagtttccac	tcctgcttta	ctcagttctt	44040
gtgccgtttt	ggagctaata	gtgagattcc	tagatgagga	cgcaagtagt	ttaggcttca	44100
agaataaagc	atctctgtca	taaacacgga	atctggaagg	cttggtgga	cccaagcttt	44160
gccgcggtgt	ctccttcctt	tcccatccac	aagaagtaac	ttgagattgc	tctctacctc	44220
cttgaccagg	gctggctcctg	gatctgaaga	ctggaacagt	gaaaaaggaa	ggccagcagt	44280
cttccatgag	gatgtgcatg	ggctcacgaa	ggctggtcat	ctgccgcatg	aggtgtggtg	44340
cttgggattg	tgttgggtgg	gaataagagc	agctaaggct	tccatttctg	tcagaggcat	44400
tagttagtat	ctagtatcta	gagctacgtt	ccttgccaca	gttggattac	atttaacttt	44460
caagaaccag	ttgttttacc	atacttataa	tatgtaagag	aataacagtg	aattacagtt	44520
aaggcacagt	tggtaggtcc	tttgtgttga	cttcttactt	ctgtcttagc	ttcactactg	44580
ttcatagggt	aagagtcaac	gttcattatt	ttgttcaggg	gctagagaga	tggtctagca	44640
gttaagagca	ccttttctgc	ttccagacga	cctcagtttg	aattccaaca	ccacatggca	44700
gtcacaca	tctgtaactc	cagttccagg	ggaatctgat	ttctctcttc	tcgattctgt	44760
gggcatcagg	catgcatgtg	gtgcacagtc	atgcaggcaa	aaaccatac	gcattaaaaa	44820
tgttttaact	ggatttaaga	tgtgggagag	ttgtcttact	agttaagagc	acttgttttg	44880
ttcgtctaaa	ggacttaggt	ttcttttgta	gtacccatgt	gggtggctcac	agccacttgt	44940
ggctccagtt	ctaaggggtc	tgatatactc	ttggggccagc	aggccatata	catgggtgcat	45000
atatttgcat	gcaggcaaaa	cattcataca	cataaaataa	aaataaatct	ttttttcctt	45060
tttaaagtga	atgcagaaat	tgagagagata	gcccagtact	aagtgtgtga	tgacacaaaca	45120
tgaagaacct	gagctcaatc	cccagcacct	atggaaagtt	agatagtcctc	atttctggag	45180
aggcctagcc	aaattaatga	gcctcaggtc	ctagttagag	accctgtctc	aaaattcagg	45240
gtaggagggg	ctggagagat	ggctcagcag	ttaagaataa	tagctgctct	tccagaggac	45300
tggtcaatt	cccagcatct	gcatggttgc	tcacagccat	ctatgacccc	agttccaggg	45360
catcggatac	ctttttcttg	ttcctgtgta	tccaggcgtg	cacgtaatgc	acttagagac	45420
aggtagagca	ttaatacaca	tttcaaaaga	attacgatgg	agagctcttg	aggaactaca	45480
tgtgaggctt	gtctctggcc	tccgcatgcc	tgtgcgtgta	cagcatgaac	atatacatac	45540
atatacatgg	atcaagaaac	cggctgcaga	gatggctatg	cagggataag	agattatatt	45600
gctcttgcat	aggactagct	ggggttagtt	tcccagcatt	cttatcagat	agcttgtaac	45660
catctgtgct	tctagctgca	aggagattca	aagcctccag	cctccacagg	tagctcaaca	45720
tgacataact	ccctctcttt	tccatgcata	cagctaaata	aaataaatct	tacaaaacag	45780
aacagatgtg	ctagaaagat	ggctcatcag	ttaagggccc	taactgctct	tctagaagtc	45840
ctgggttcaa	atcccatcac	ctaattggcag	ctcgaaactg	taactacaag	atctgacgct	45900
ttgacactga	catacatgca	ggcaaaacac	caatgcatat	aaagtaaaaa	caatagacaa	45960
accgagtgtg	acattgcttg	tcttaaatca	tagtgctcag	gaggcagagg	ccggcatatg	46020
tgagtgaagc	attaggttct	cgagatcacg	agactgatag	agaatcttgt	tttagttcat	46080
agcagcagaa	ctccaccatt	gatgtgtatt	cagacttaaa	actcaagact	gacctgcttc	46140
atcatccaag	tgctgagatt	ataggcggtt	tttgtttgtt	ttgtttttca	gattaaaaaa	46200

-continued

aattatgtgt	gcatgatata	tgtggatgtg	gactcgtgtg	tgggtgttgg	ggtgcaagtt	46260
gttgggtctt	tcctacaaca	ctgtgggttg	aggtaatcaa	atttaggtca	tgaggcttgt	46320
cacaagcacc	tttacctgat	ggccaatctc	cctggctacg	ttaaaaaaaaa	aaaaaaaaaa	46380
aaagagtttc	tggcagaggt	acaaaattga	ctattccata	gtttaatagt	ttagaggagc	46440
cgctggaatc	aggctactct	ggtttatttt	gaggggggtg	ggtcttatta	tgttgtccag	46500
gctcatttaa	agatcctcgg	ctcaagttat	cctccatttg	agtttcctaa	gtagcttggg	46560
tctacagaag	gtatatcact	gtagttgact	gaatgttggg	atttgtttag	ggatgggggc	46620
tcactgtgta	cccctggctg	ttctagaatt	ggctatgtag	gacaggctga	ccttgaaatc	46680
acagagacct	gtctgactgc	ctcccaagta	agttgtttga	atccatagta	ttccctggat	46740
ttgaattcta	atttgatact	ataagacttg	tgttgctttg	atgtcatcat	ccactattgg	46800
aggtgagact	gtcaaacgta	aaacattgtt	atcaggatta	gctcgattga	tagtatgaaa	46860
atactttaa	aagaacgttg	aggcaggagg	attcctacaa	ggccagtatg	gcctatatag	46920
caagttctgg	atctcctggg	ctatatagtg	aaaccttgtc	tcaacaacatc	aatctagatt	46980
tgggtgtgca	tgctgtaat	cccagaacct	tggaggctaa	ggtaggaaga	tcataaattc	47040
caggctagaa	tgaactacat	agtaagacct	tatctctaaa	aaaaaaaaaa	aaatagagaa	47100
agaatagaag	taggattgga	gggcgtatct	tgtggacatg	gtaagcctgg	agtaagggtga	47160
ataataatga	aatatagcac	acagagatga	tatgcttaga	gcagaagtca	gagaacagaa	47220
gttcttattt	gtgactaaag	cttcattgca	ccatagctct	tcctgtgtga	acacttgctc	47280
tctttggctg	cttttatgct	tgattgtctc	gaattgtcta	gttaaaagac	tgtgtgacca	47340
tcagactaaa	accacttact	gtctagtcat	tcacagaaaa	cagtaaaaca	gtcaccaact	47400
cctgatgtaa	aaagatggca	tttgaagagt	gtatgcaatt	gttttagttg	gagttttagg	47460
ccaattaaaa	gttttaagg	agtccaaacc	tttcatcttt	gtcctctctg	aggctaagga	47520
aagaggatct	caatcaagat	caaggccagt	gtgggcaact	tggtagctc	cagtccaaag	47580
ttagggaaat	aaaacataaa	aggaggactt	actgctcggg	ggccagaggc	tcgcctggca	47640
agcacagaaa	cagctcaata	ctcagttttt	aagtaatcta	ctaactctgt	tggcctgggtg	47700
gtactttcta	tatctcatta	cttgggactt	aaaggcaagc	agacagtttg	tgttcattct	47760
gtgtgttatg	agatcctggt	tcaaaaagtg	gtctgggttg	gaaaccagag	atagatagct	47820
tagtgtaagg	aaacttgga	gaaagcctga	taatacacgg	ttgattactg	gaacctacat	47880
agggcatgca	cagagacaga	gacagagaga	gagaccgaca	gacagacaga	cagacagaca	47940
gacagacaga	cagacagaca	gacacacaat	cagccagggt	cgggaatata	atatggcttg	48000
gttggtagag	tgcttgtcta	aaatgcattg	agtcattggg	tcaataccta	acaccgactg	48060
gtatgttgat	acctgcctgt	agtgccatca	ctcagggtgct	gttgatcaaa	gggtcagaag	48120
ttcaaggctc	tccttgggca	catagaaaagt	ttcaaaccag	cctaagcctg	aagggtgctgc	48180
ctcaaatata	acaaaacaac	aagcaaacaa	aataatagaa	ggtttttcca	tctcagcctg	48240
acttttcttg	ttacttacta	gttttcagt	tgtagttgga	tcttcttatt	ctgttggttac	48300
tgtttcccat	agcccagcaa	tttgcatctt	ctgtttgttg	acagggtgtg	tactagctcc	48360
gtggaccctg	tttccatgaa	tagactgagc	tttttgagga	acagatgcag	gtaagatctt	48420
aggcagtgga	gatcaagaga	tgggattttt	accttctcta	ctggctctca	ccttctttta	48480

-continued

cctcacgggc	acttacccgc	tcacaatgtg	tttctgaact	tactgaatag	atcaatccat	48540
ccatcaattg	attgactgat	tggtttttct	gtgacagggt	ttctctgtgt	agccctggct	48600
gtcctgaaac	ttaatctgta	gaccaggctg	gtcctgaact	cagagatcct	gagtgtctgg	48660
atcaaaggca	tgcaccaccc	tgccgtgatt	gtttctgaac	tttaaaagct	tctcttggtc	48720
aaggaagttg	cttactatgt	tacctatfff	tctgtgtgtg	tttatttcaa	caagggtctg	48780
tgagcatcc	acacacgtac	cagtaataaa	tgataaata	aataaataaa	taaataaata	48840
aatgctttta	aaacacaggt	ttcctttgta	gaatttcacc	cgggattcct	ataccttttc	48900
taggaatggg	cttggtctg	tgaaggaagg	agaacctcac	ttgtggtag	tccactgcac	48960
aggctacatc	aaggcctggc	caccagcagg	tagggaaaat	atacagtaat	ttctctctgg	49020
tatatgttgg	tacataaaca	attggcaata	tggtactaac	agttagcaat	actatgtacc	49080
cctttatgaa	atgtgcttaa	gaataattca	aaagatagat	agacaaataa	aacagactcc	49140
ctctcatctg	ttaccaatgt	tatagtctat	ttgagcatat	ggattactaa	aacataaaaa	49200
tgactcaata	ttagctttat	tacaaaatgc	tgtaggtttg	ttttcgaagc	aggtttctct	49260
gtagccctgg	ctgctttgga	gctgactttg	tagaccaagc	ctcatttcca	ctgcctctgt	49320
ctccccagag	ctggattaac	taaagcctac	accacaactg	ctcaaccttt	tttttttttt	49380
tttttttttt	aaatgtttta	ttgggagctg	gaaagagggc	tcagcagcag	ttaagaacac	49440
ttactgctct	tcagaaaaat	ctgggttcag	ttctcagaac	ccacatgttg	gcttaaaaact	49500
gcctataact	ccagtttctt	gtgatctgtc	actctcttct	ggcctctgca	ggttcctgta	49560
cttatattgt	gtccataaat	tcacacaggc	aaatacacia	aaacaaatgt	attactgatg	49620
cttatcccta	tatttatagt	agataaatat	atatgtaaag	tagatacttt	tcattctctg	49680
cctggaactc	ctattttcag	caattttctc	ttcaatacct	tctctgggaa	ttgcaagcat	49740
gagctgctgt	agttggtgta	gaattcagtt	attagtgtct	agaatatagc	tcagtaatat	49800
agtaactgcc	aggtttatgt	caggaccaaa	acaacagaa	aaaacaagcc	agtgtgtggt	49860
ttaaaataat	tctcaagtat	aatagtagta	tacactgaat	actgtgtctt	taagtagctg	49920
tgccaaaaca	aacaaaacaa	aaaaaaacca	ctggagtttt	attttatttt	ttgggtctta	49980
gtgtattcct	ggctgcctct	gagctggcct	cagattcaca	gagatccacc	tgccctttat	50040
gtgctaaggg	ctaggataga	aggtgtgtgc	cactatgccc	agcttgaaac	attggtattt	50100
aatgcaatta	atttgggcaa	gctgaaatgg	aagagaaaact	ttaagcaatg	aatgcaatgg	50160
ctttcttgca	gtaactttta	aaggagaggt	tctcttgaaa	tgtagtcgt	gagtagagta	50220
gctttatttt	aatttgagat	taactaaggg	atgtagcaaa	agaggtaggc	tgtggggtca	50280
gacttggttt	ttagatcatg	gccatgaact	ccttacctca	gtctaacaaa	tctgaatta	50340
cgggctgggt	ctccatgccc	agcaaggcca	gctttttaaa	ctgactgtca	actttccaga	50400
tctcaccccta	ttactttcct	actataaaaag	gattgctggg	aaatggggat	ttacagaaga	50460
cagaaatgca	gagaaaagag	agacagggtt	ttaatactta	gttgttttgt	gtgtggtagt	50520
gtttctgtct	catatatgta	tgtctgtgca	ccacttggtt	gtctggcgcc	cacagaggtc	50580
agaagaggat	gttgaatccc	ctggaactgg	aattacaggc	gggtgtgagc	tgccatgtgg	50640
gtaatgggat	ttgagcctag	tctggaagag	cagccagtgc	tcttaaccac	tgagcctttt	50700
ctcagcttcc	ttttctcagc	tgatatatft	taaaaggaaa	ttaacattga	tttgtgtctt	50760

-continued

agggtttcta	ttcgtgcaca	aacatatgac	caagaagcaa	gttggggagg	aaagggttta	50820
ttcagcgtat	actttccaca	ttgctgttta	tcacggaagt	caggcctgga	actcaagcag	50880
gtcaggaagc	aggagctgat	gtagaggcca	tggagggatg	ttccttactg	gcttgcttcc	50940
cctggcttgc	tcagcctgct	ctcttataga	accaagacta	ccagcccaga	gatggtccca	51000
cccaccaggg	gcctttcccc	cttgatcact	aattgagaaa	atgccttaca	gctggatctc	51060
atggaggcat	ttccccaact	gaagctcctt	tctctgtgat	aactccagct	gtgtcaagtt	51120
gacacaaaac	tagccagtac	gatttgggaa	aaacttaata	tttgcctctc	ggcatttgtg	51180
aatagtttaa	cctatggcaa	gtttcttgac	ctttacatgt	tttccttat	ctgcagtcca	51240
ggtcatacat	cctgtatata	atcatcgtga	gttagattta	gtgtaaggaa	agaacacccc	51300
agtgcctggc	acatgctcta	tagccaagaa	atgggaatta	ataattgagg	aatattatg	51360
tatagtggca	catgaactgt	tgagttaact	tcctatgtaa	atcatacctt	tactgtatgt	51420
atgatctttg	atacttctgc	atagctgtcc	tagataagaa	tgagagataa	agacattgtg	51480
agggatgaac	tcttattccc	tttttctgtg	gaaatgaata	tcttttgggtg	ttgggacaat	51540
ttaatttttc	tttactttta	aaatcactgg	ttaggcagga	atatttactt	ctctgtgtat	51600
gatatagtca	catagcataa	gtaaaagtta	tattttttaga	ctcctttgat	tgggacttgc	51660
attttcaaat	ttcttaaaat	ggttaaagcc	aggtgtgctc	atatgcctga	aatcctgcat	51720
tgaaaagatg	aagagtccag	gttacacaca	cacacacaca	cacacacgca	cacactcaca	51780
cgtgtgtcac	atgaaacagt	aactgggttat	tttattaaat	cttagcatct	tcatagggaa	51840
atagtgagtc	ttcagtgact	tgcccttaaa	gggatttgaa	tttgtgatct	ctctgagtca	51900
ttctcctttt	tcttcatgaa	gggtgtctcc	tcccagatga	tgaccagag	gctggccagg	51960
ggagcaaatt	ctgcctgatg	gccattggca	ggctgcaggc	aagtatgagt	cttcacatct	52020
atgtcctttc	agtttaggga	aaaaaaactt	ttcagatttt	atttgtggta	attatctttt	52080
gctctgtgaa	tacatagaaa	aattccataa	aactcaagat	ctaaaataat	gtgatattta	52140
taataaacat	tgctattctc	agacttagct	aaaatcaaaa	gcatgagaga	gggtggtaat	52200
cttgtgtgtg	ttgatcttgg	taatgactcg	tcctgtttac	ctaggcctcg	agctccttgg	52260
ttcaagggat	cctcccccta	aagcctcctg	catgttggga	gagaggcagg	cgtccgtcac	52320
catgccaggc	tccccctggac	attgttagtt	ttagctttac	agtacttact	tttctatttc	52380
caattaattt	cttttgttcc	tatgcaaagt	aagaacaatc	atttttatta	tgteattaca	52440
ttctttataa	tagactctaa	atatcttaaa	atttttattt	tatgtgtatg	gggtgtttgc	52500
tttcatgtgt	gtctgtgcac	ttgcatgcct	ggtaaccgag	gaggctagaa	gaggttattg	52560
aatccccctg	aactggagtt	ccagaaagtt	gtgacttgac	gtatgggttc	tgggaatgga	52620
acgcggttcc	tctggaagc	agtcagtgtc	cttaacactg	agccgtctct	ccagcccttg	52680
attttgatta	ttttcatgaa	ccctgttcag	tttctcagaa	acttgaatca	ctctgaataa	52740
tgaatacggg	ctaaccaaat	aaaaagtagg	tggtttaggg	taacattcac	tattttctta	52800
ctttaccaac	ttggtaagag	aacttacata	ggagtagagt	tagagtatat	gcctgtcggt	52860
aggattgaca	tttttgcat	tctgggtaaa	acttctaaga	agtttctaaa	tctggttagtt	52920
tcatatctac	acagatactc	atgaaatatt	aaaagtattt	atgtaagtaa	tggtgttatt	52980
tgggctcatt	ttatctctcc	tttcttaggt	aactagttct	cccaactgta	cagacatgag	53040

-continued

taacatttgt	cagccaacag	agttcatctc	ccgacacaac	attgaaggga	tattcacttt	53100
tgtagaccat	cgttgtgtgg	ctactgttgg	ctaccagcca	caggtgagga	gcgtagcttc	53160
tgcattagta	acacgttagc	ctctgttttc	tgttaccagt	gttgaggtta	catggctaata	53220
tccagagatg	acaaaaatat	agcagtccag	ttcagaaaaa	gagatgctcc	tattttgcga	53280
gtagcaaaat	atagtctcaa	cttcctttca	agactatcac	tccatataga	gaaatgtagt	53340
tggtaaaacc	atatggaaat	agtaggtata	aatatatagt	ttttattact	aatgtcaata	53400
cagatcattt	aaaactcctt	attttaatta	ttctagtata	actagaattt	atataattac	53460
tatattttag	taattttatat	aattactagt	agaataagcc	tataataatt	ataagtgtag	53520
cactgcttat	taaaattctc	atacagtagt	atatcagtta	actaccctcg	acttacatgg	53580
acatggtctc	tgttatttat	gagcgtggct	atgagtgtgt	gaagtggtea	gtcaagatgt	53640
catcttgggg	gctggagaga	tggcttagtg	gttaagagtt	caaatcccag	caaccacatg	53700
gtggcttata	accatctgta	atagatctaa	tgcctctctc	tgggtgctct	gaagacagct	53760
acagtgtacg	tatattaat	aaataaataa	ataaataaat	ctttaaaaaa	aaaaagaagt	53820
tgccttgaaa	atgaagaagg	tgggagcag	gtggtgtatg	cctttaatcc	cagcacttgg	53880
gaggcagagg	caagccgatt	tctgagttca	aggccagcct	agtctataga	gtgagttcca	53940
ggacagccag	ggctatacac	agaaaccctg	tgtcaacccc	cccccccaaa	aaaaaaaaaa	54000
gaaaatgaag	aagaaagttg	gagaatttac	ttacaccag	atccaacact	cctgttaaag	54060
gtgctgttat	taaggctgtg	tgggtttaat	gtactgatct	attctcatga	gtaagctaaa	54120
gagtcttttt	tgcattggta	attggatttt	cagcaaagat	gcttagacat	ttcaagggga	54180
ttctatatag	accacagcca	ccaccctaa	aatcatcat	accatagaca	aaaatcgact	54240
caaaagcccta	aatgtataag	tactaattgg	aaacaccttt	tagaagaaaa	tctttatgct	54300
cataggtgag	caggccgcgg	cacaccttgg	gagggtggga	ctcaccgggt	gctattcatc	54360
tttttgtttt	gaggcaagat	ctcccattgg	actagaactt	gccagtagt	atagacttgc	54420
tggccactga	gctcccataa	tccactgtct	taagattatg	agaatatcct	acacttgact	54480
ttttgttttt	tggaaacagt	gtctcactcc	attgcttttg	gtactggagc	tctttataga	54540
gaccaggctg	gcctcaattt	cagaggtctg	cctgcctctg	cctcctaagt	gctgagatta	54600
aaaggcctgg	ctatttttta	tttttatttt	atgtatatat	gtgagtgcct	aagtatatga	54660
atgtgtgcca	tgtgtttact	tagtaccaga	aagaccagaa	aatgcgttg	gtctctctga	54720
aactggattc	taggtgggta	taacattctt	gataacaact	gctctacagg	aagtgttggg	54780
tcagggattg	taaatttttc	aacttagttc	ttcattttta	acgtctgggt	tgtgatcttt	54840
gcaaatgcag	gaagtgtttt	taagggatga	gccatctctt	ctgctctgcc	atacccctac	54900
ctttttctat	ggtttttgaa	aatgtattct	aaggaccaca	ctcagctcct	ctaattgttat	54960
ctacaggctt	agctctttcc	atccctccgt	cctcctaac	tcccatcttt	ttctaggcta	55020
gcctcaaaact	ggaaatcttt	ctgtcctagc	ctgtgatgct	gagattagag	tatgccacta	55080
tgcctggcaa	aaattttctc	taaaatgata	tcattaaaag	agctggtaaa	gtgattttgt	55140
gagaaaggcc	tctttgtttc	tagttgttcc	attacattct	tcaagcacac	acgtgaccca	55200
tagagtccaa	gtgtgttttg	gaggacactg	agcaggagtc	agctccccga	gttgggttcc	55260
agagatggac	tcactgaacc	atctactggc	cctgcttctc	cacacaccta	tttatagtag	55320

-continued

gataaaagaga	agaagtaaca	tccatatctc	taacagatgg	gaaggcgggt	ttattttacg	55380
tctctccttc	ccttctagga	gctcttaggg	aagaatattg	tagaattttg	tcctcctgaa	55440
gaccaacaac	ttctaagaga	cagctttcag	caggtaacat	tttctcgggt	ttgatctgag	55500
tacataatctt	gatcaattct	tcaagtttat	tctagatact	tactgataag	tggtcagttg	55560
agcactgtgg	tggaactat	ctacctatct	taattttctaa	aaaatataaa	atgataatac	55620
tttgaaacta	gacaaagtcc	aaggatattc	tgctttgggt	ttatccaata	aattctcttc	55680
aaagcattta	aaatattatc	tgcttaacta	ctttatttta	gattatagca	gaaaaattgt	55740
ctcagaattc	ttttctctat	aattgaaagt	taactcacta	gtaactcact	ggtaacttgc	55800
tgtagttctc	aggcacgagc	tcttgaaaac	actcggagac	gataaatggc	cttggtctta	55860
gataaacagg	ctttatatct	tgtaagttaa	ttaagtcttg	atactgtgct	tcctgatata	55920
atggctatag	taataactta	ggtagaagct	tgtagggagag	tcaagtatgg	taaagccata	55980
ggcacatata	tacatatggc	ccagcctttg	acacatgttc	attgctaata	tctttattgt	56040
tagagatgga	taactaagag	attgtcttct	gttcataag	acagaaacta	aaacattaac	56100
atagtacttc	tcttaggggc	tttgtggaaa	ccaaaattgt	taagttttga	gttgaagagc	56160
tgggattgct	aagtaagggt	taaagtgtat	ttagtgtcac	ccacctgggg	ttcctggtat	56220
taacctagaa	agccagtttg	ttgagaatgt	ctgcatacaa	cttcaaggaa	acatggagac	56280
actcgttctc	gtgttccttc	ttcactgtac	agtcatacag	gctgcagctc	tggaagata	56340
cctgatagat	agatgcccc	cttaatttcc	tcttctcgt	ttgaacgttg	aaaaagactg	56400
gtgcttcagg	ggcaacaaca	cgagtcctaa	ggctgtaaac	atggcaagat	tattacttaa	56460
ttttcttttt	ttttaagtcc	actgatggat	gaaaccctt	tcagggtggtg	aaattaaaag	56520
gtcagggtct	gtccgtcatg	ttccgattcc	gatctaagac	ccgagaatgg	ctgtggatga	56580
gaacgagctc	ctttaccttc	caaaaccctt	attcagatga	aattgagtat	attatctgca	56640
ccaacaccaa	tgtgaagtat	gtacccttca	gtctgcccc	gtgttgggtt	cttcatectg	56700
tagccactcc	taggggtggg	tggtgggtgca	gcagggcaag	tcttagcttt	atcatgctgt	56760
cttctcttca	gcttgaactt	actaaataac	atcagtttga	gattctctcat	ttaacattta	56820
aatttaacat	taattgaaat	tcctttctat	aggagttagt	gtagttaggg	tagagaacaa	56880
ggtgggtttt	agttgctgtt	ggtatctact	ttctaatttg	tgtatgttga	atgggcccgt	56940
aatagcatgt	gtgaacatca	gagcacagct	tgcagtagtg	ggccccctt	tatcaagtag	57000
gtcgcaggca	tggaattcaa	gttgctcagct	gttggtggc	acttttccta	ccaggccatc	57060
tcattggctc	acggtggaat	aagtgttaat	aagcagcagt	agttggtgct	gtgagcagag	57120
ctttcactgc	tgcccagcct	tggtgcccac	tgcagtgtgc	tcagccaact	tgttttctaa	57180
aaggctgcaa	gtaaaatttc	caaagattag	atttttttgt	ttttcttct	ttttggtttt	57240
acgagacagg	gtttctctgt	gtagccttgg	ctgtcctgga	actcactttg	tagaccaggc	57300
tggtctccaa	ctcagagatc	cccctgcctc	tgctcctga	gttctgggat	taaaggcatg	57360
gaccagcact	gcctttcttg	ttgtaaat	ttatataata	tattctgatc	acactttccc	57420
cttctagctc	cttcagatc	ctcccaccta	ctaaactcca	tgacctacac	acacccgaga	57480
gagacagaga	cacagagaga	gacagacaga	cagacagaga	gacccaaaata	tataaacaaa	57540
agaccaata	agacaaaaaa	aatgcctgaa	cagagcaaga	tgagataaaa	accctgtaaa	57600

-continued

aatatcactg aatacatagg ttacctatgg gactggacta agatgttagt aattgttcac	57660
cttttagtcaa tatatggagt ttattgtatt gagtaattcc ttgtttcccc ttttgtgttc	57720
ttgtctactc tattttccta ggaactctag ccaggaacca cggcctacac tgtccaacac	57780
catcccaagg tcacagctag gtccgacagc caatttatcc ctagagatgg gtacagggca	57840
gctgccatcc aggtaagaaa tggtgaaata gttagctttt caagtaaaaa ctagctgggt	57900
gtagtgatgt gcaatcacat atttttgttg ttgctgcatg tggtttattt tttaaagtct	57960
ttttctccaa attctttgtt aaaagtctaa ttttcccta tctgtttcca cactgatgtt	58020
tgacgtatag gcagcagcag cagcagcaca cagaactgga tatggtacca ggaagagatg	58080
ggctggccag ctataatcat tcccagggtga gtgtacctt ttcctataag gagacaatga	58140
acattttctt aaaatgtata ttgaagctac cagaatggtt tagtggttaa gagagtactg	58200
ctcttgga aagcccaaat tcaattccta gtaaccatag tgggtggctc acaatcacct	58260
gtagacacta tgttcatata cacagacaca gacacaacaa tttaaaacaa aaatgaatct	58320
taaaaacaat atttatcagt gccagtgaga atgttctata taaaattgaa cattattgat	58380
tgttttcaact attttatcc ataggtttct gtccagcctg tggcaagtgc aggatcagaa	58440
cacagcaagc ccttgagaa gtcagaaggt ctctttgcac aggacagaga tccaagggtt	58500
ccagaaatct atcccagcat cactgcaggt atgggtttct tccgcaggct ccttttacag	58560
gctgagtttc attattactg atgggactgc ccagtcagca tacttctact tcagttacag	58620
tacttcatga ataagtagga attgattaaa ctatgtgcta cagccccttg atggccctcc	58680
cccaactcct tttggtctgc agatcagagt aaaggcatct cctccagcac tgteccctgcc	58740
acccaacagc tgttctccca gggcagctca ttcctccta acccccgcc ggagagaaat	58800
ttcaggtgag ccccatatgt gtgtgctgct tgacagggt ctgcagggtt cagttgctgg	58860
atcctgtgt catcttcct tcttttctt ggtcacctca gacaaagcag tagaacttac	58920
tggacctagg gtgagacaac gaagctgctt ttcctcctgt ttttgacct attctattgc	58980
cttgctctag gttccaaacg tctctgtgtg gtcagtgtgt gacagtcagt ctttcttgtg	59040
tttttaaatt tatcaggttt tccttaactc caagaaatca gaggaatcta gggatagaat	59100
gtgtcctttg attcatagct tctgtgatgg agtcaacct ttaacctca ctttctattt	59160
gttccttct aggaatagtg gtcttacct tctgttaacc attgtccagc catcatcttc	59220
tgcagggcag atactggccc agatttcag tcaactcaac cctgccagg gatcagcgcc	59280
gacctggacc tctagctccc gccaggctt tgcgcccag gtacgcctc ttacctgtct	59340
gacctgtgt gttgtgttt gtgggatctt tttttttcc tccaggtaaa tttattattg	59400
tcagatacct ccttttcagt tctgttctt catcttttaa tttcatctt tttgcgagg	59460
agctagataa ttaaaatacc agagataaca tccagaagtc tctttagaac ctatgttttc	59520
atatgctcac cttaagacag aactgctcat tcacagcagt ttgaacagct ttggtctcag	59580
gcttgttttg agtaaatca aagagtttgt cttgttttag gactatgtaa tatagtacca	59640
aagtagaaaa ttagtaatta tattcattta tttatgaaaa tatagtatcc atctatataa	59700
tatatagtaa atatgttaaa tttatttatt actatgtatt tctcttgtct atataataat	59760
ttagaaaagt ttaaaaaaaa atgaaaactc aaacttgact ccagaattgt tctctatagc	59820
tttttgtgt atgtgtaaaa atactcagga atgttgccca tgactcttg tcaggatgtg	59880

-continued

ccgtgatggt gatgacagct gctaccatgg ttttcatact ggtgacataa tcaagcatgc	59940
atatattatc tcccttggag ttacttttta aattgtggat ttaaaacggc ctctagaaat	60000
tattgtatct cacaaaaaat gtttagaggca ataactagtt tcttaatcaa tatacagtaa	60060
atgggtgtga gaaaggacag ctttaatttc aacaaagaga ctgaggcagg agcatgggcc	60120
tgggccacat agtgagagat aaactgtctc ataaaagaaa gaacagaaca aaacaaaaat	60180
agcataatgg aaaataaaag aggacattgt ccactgtgcc aagtaacagt ctcttctggt	60240
ggggttaaca gtgaggtttc atttctagtt tattttttcc aatttttttc tattcttttt	60300
gaggcagatt tagaatttat attaaacaac cctttgcaga ttactactta aagtcaagag	60360
caaaagagaa gcactcagaa ctgagtgtgg gtgtgaactc cctaagatgc caccaaattc	60420
ctctgtaaca catagggatt ccagtaaaaa agaaaatggt tgtgccttta ggaaaaggat	60480
ctagaaacgg gtgcagtgtg gagtgagtgg tttctctttt ataactctct accattggga	60540
cccagagat gacgccattg ggaaagtgtt ttgtcacttg agcctgacct gatgacctga	60600
gtttaatccc caatctcctt ggggggaaga gagaaccaat tcttgcattg tgtcctctaa	60660
catgctgtgc agagcatgca tgtgttctca tgtgcataca tactcatgca cactaaaaat	60720
aagggtgaaa cctttaatac caccacttgg gaggccaatt caggtagatt tctgagtttg	60780
agttcagcct ggtcttcaga gtgagttcca tgacctcaga gaaatcctga ctccaaagac	60840
aatagaaaaa agaaataata ataataatgt ggaaaataat aaaggaaaac acccagtgtt	60900
attgacatct gtgtgtacat gcaaccatta tacagagaca tgcacatgaa cacacacaaa	60960
tgaagtgaag acatgttgat ctctgggttc cattaatattg tgcacaatag cctgtacatg	61020
tatgttgaac ttggacacac atggatgtta tgctttctat taattgccat aatttatgag	61080
ctgattatat ataggaatag tttttttttt taagatttat ttacttatta tatgtaagta	61140
cactgtagct gtcctcagac acaccagacg agggcgtcag atctcatttc ggggtggtgt	61200
gagccaccat gtggttgctg ggatttgaac tctggacctt tcggaagagc agtcgggtgc	61260
tcttaccac tgagccatct caccagcccc aggaatgggt ttttaataat gttttcatgt	61320
atttatatag tgttgttttg ggttttttgg tctttttgaa atagagtttc tctgtataac	61380
agagtcctgg ctgtccttaa cctgacttaa tagaccaggc tgacctgaa ctcaacagag	61440
gtctatctgc ctctatctct ccttcccgag tgctggctgg gattaaaggc atgtgccacc	61500
acactgaccc gtatacagtg tattttgatc ataactgttt ctactccaga ccagtgatgc	61560
ctctccctct tacciaaccag tccctcttgt atgtcagtgt ctctttccca tttcatgatc	61620
cagtgtgact aattatcaca atttgtaatt ctttgttttt ttctttttca cttttatttt	61680
agtttcttaa aacatttagt ttttaggaaga attgggagtt aatcagaagt atacattaga	61740
agcaggtaat ggggttgggtt tggaagaagg tagtggttga tgagtatcga cttacaggaa	61800
tgcatgacac gattaacaat cctttgttct gtacccctct ccttttagcag gtgcccaccc	61860
aggctacagc caagactcgt tcttcccaat ttggtgtgaa caactttcag acttcttcct	61920
ccttcagtgc tatgtctctt ccgggtgtct ccactgcctc atctgggtact gctgcctacc	61980
ctgtctctcc caaccgtggc tccaactttc gtaagtgcag acaagggaga taacaggaaa	62040
atcaaaactac taaagaagga ggacttggca gttatgattg ttttccctgc gtcctgcatg	62100
tgctgaccga attataagga aatgcatggt ccaggctctgt ttgattttta acagccttgc	62160

-continued

atagggcctg	ttgaaatggc	tcattgtgca	aagtgtctga	cacacaaacc	gggtaacctg	62220
agttcatatc	caggagagag	ctgacgccac	catgagctca	catgcaccat	acacaagaca	62280
gtaagaatct	taagaatcat	tataaaaaa	tggatatagga	aaaccattta	actcctgtag	62340
ttaaagacca	tgtgaatcat	tttaatatgt	ataacaatct	tacttaatag	actgcatatg	62400
taaatgaaca	aggaattctt	cagaaatgct	atctaggaaa	tgaaaacttac	tgtgagactg	62460
agttttgaaa	atagaagcag	ccctgaccag	cagagagaag	agcagaaggt	agcatatgga	62520
gactactgac	ttacacgtag	ttgtgtgctg	gtttctcttc	tccattacaa	ctataaatgc	62580
ttattcttat	ttctagctcc	tgagactgga	cagaccacag	gacagtcca	ggcccgga	62640
gcagagggcg	tgggtgtctg	gccacagtgg	cagggccagc	agcccatca	tccgtctagt	62700
tccagtgagc	agcatgttca	gcagacacaa	gcacaagcac	ctagccagcc	tgaggtcttt	62760
caagtgagtg	ggtaaagact	tcagagagag	atcggtcagg	gaagagagga	agaaagaagc	62820
acatggtatt	ggttagggct	gaacggaatg	agacagagga	tgcatgtcag	cagttgaagc	62880
aattataaac	atagcctgta	accagaccag	gcagaggtac	tgatgggaag	caacatgcaa	62940
agatgctaaa	gaaaggtatt	ttaattttat	acagagattt	acatctcaa	gtagtagtta	63000
tggatttaaa	tagaagaata	cgaaaatata	tggagtagaa	catactgatc	atagctataa	63060
gtatctgttt	cctttgaggg	gcctgcaaga	ttgaatgtgg	tcctctcaga	gaagccagtc	63120
agaaagacca	aaggaaggca	acataggggt	tgattgagaa	cagatgtgat	taggcacatt	63180
tcagatgtgc	ctgtaggagt	taaatgaaat	gttggtcatgc	atatttcttc	agttaaaaat	63240
attgagtaca	agaaaagagg	aaaataaatg	atctcagagg	aagatagaac	agagaatgag	63300
gaaagagttc	tcagaagagg	gaggttgaga	gaactcgcca	tgacagactg	tgccggtcag	63360
gaatggtggt	ggtgtgggtg	ggggaagggg	gtcctggaag	ggaactcact	aaaataaggg	63420
tatgtgaccc	aagtctaccc	ttttctcat	taggaaatgc	tgtccatgct	gggagaccaa	63480
agcaacacct	acaacaatga	agaatttcct	gatctaacta	tgtttccccc	cttttccgaa	63540
tagaactatt	ggggtgagga	taagggtggg	gggaaatcac	tgtttgtttt	taaaagcaaa	63600
tctttgttaa	acagaataaa	agttcctctc	ccttccttc	cctcaccct	gatatgtacc	63660
ctttccccc	cttgacttgc	tgaagaaacg	ttatagaaga	aattaaatga	atttcccagg	63720
cttttaggat	cctctgaaat	ttttaggata	ggtgaggcct	gaattcctgt	ccttatttct	63780
tctgaccaga	agttgcacag	acatgatttg	tgctggagtc	aaggggcaga	acagaagaat	63840
ctgacaggca	ctaattggat	actgtggctt	gtttggatag	aaattctgaa	tggagtggag	63900
gaaaggagaa	atgccctcat	cactgaggat	catgaaacac	agtaggggtg	tgtggagcct	63960
tgggacgtga	gcagtctcca	gaaagaggcc	tgagagagag	catgaacact	tatctttgtg	64020
agtgagttag	tgagttagtg	agtgagtgtg	tgtgtgtgtg	tgtgtgtgtg	tgagagagag	64080
agagagagag	taagagacag	agacagatgg	ggtgaggggg	gcatttgagc	tccatgtttt	64140
tgttccctat	tatagagtat	atgcaaaatt	tgtcccagat	cttctttgac	tttgtgcttg	64200
ctctttaaag	tgtcctaaga	aaattaattt	tttcaggtat	tttctattt	agtgttgacg	64260
ccaaagagta	tttaaatata	gtctttgtctg	cacttaaat	cataccagc	caaaatggaa	64320
ctttaggcca	accccagcc	ttctgttctg	agggttggtc	tcctacagac	acagtgatca	64380
agctggatga	ctcctgctct	ttggtgcttt	caactcattg	ggaagagctg	cagatattac	64440

-continued

```

caaaataggc tggctacatg aacactgtca gaaatcccag acttgcccac aaggataatg 64500
ctgcattttt ctgtcagagt cacacatggt tttctggaga gggtatttct gcatggaaac 64560
tcaacttcct ggattagcta tcttgagtga aagtcctcac tgacgagtat gcaaaccaaa 64620
tagcctcctg cacagtagcc tctccttcct gtcacaaaaa cagttttagg tctgctgaag 64680
tctgggtgtc tttgctcctt ctgcaatcct gaaattgggg tttgctttag agcacaaaca 64740
taagtctgtg ttaggtggac ttaaatccca acagggtcac ttgataatta tagccataga 64800
aatgcagatg caggtaactg cttttaccct ttaccgtcct caggtgagtc tcttagatca 64860
acagcctttt tttttttttt tttccttaaa ctggctcctg tcaaagatta agttaatatg 64920
gaaaagacct cttatgtgta ttgatggggc atgaggagcc caggcaagga gaggctcgtg 64980
gagaggctga gggaatgtta c 65001

```

```

<210> SEQ ID NO 100
<211> LENGTH: 2557
<212> TYPE: DNA
<213> ORGANISM: M. musculus
<220> FEATURE:
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (150)...(2174)

```

```

<400> SEQUENCE: 100

```

```

ggggggggcg tccgccatct tggattccgc ggtagcgggtg gcggcggtaa ggtgcctaatt 60
ctgaggagtg gctcttcctt cccctccccc agctcgggtgg cggtgcctcc tcccaccgag 120
ggtaggcgcag ggacgggtgcc atctcgacc atg gcg gcg act aca gct aac cca 173
                               Met Ala Ala Thr Thr Ala Asn Pro
                               1 5
gaa atg aca tca gat gta cca tcg ctg ggt ccc acc att gct tct gga 221
Glu Met Thr Ser Asp Val Pro Ser Leu Gly Pro Thr Ile Ala Ser Gly
10 15 20
aac cct gga cct ggg att caa ggt gga gga gct gtt gta cag agg gct 269
Asn Pro Gly Pro Gly Ile Gln Gly Gly Gly Ala Val Val Gln Arg Ala
25 30 35 40
att aag cga cgg tca ggg ctg gat ttt gat gat gaa gta gaa gtg aac 317
Ile Lys Arg Arg Ser Gly Leu Asp Phe Asp Asp Glu Val Glu Val Asn
45 50 55
act aaa ttt ttg aga tgc gat gat gac cag atg tgt aat gac aaa gag 365
Thr Lys Phe Leu Arg Cys Asp Asp Asp Gln Met Cys Asn Asp Lys Glu
60 65 70
cgg ttt gcc agg tcg gat gat gag cag agc tct gcg gat aaa gag aga 413
Arg Phe Ala Arg Ser Asp Asp Glu Gln Ser Ser Ala Asp Lys Glu Arg
75 80 85
ctt gcc agg gaa aat cat agt gaa ata gaa cgg cgg cga cgg aac aag 461
Leu Ala Arg Glu Asn His Ser Glu Ile Glu Arg Arg Arg Asn Lys
90 95 100
atg aca gct tac atc aca gaa ctg tca gac atg gta cct aca tgt agt 509
Met Thr Ala Tyr Ile Thr Glu Leu Ser Asp Met Val Pro Thr Cys Ser
105 110 115 120
gcc ctg gct cga aaa cca gac aag cta acc atc tta cgc atg gcc gtt 557
Ala Leu Ala Arg Lys Pro Asp Lys Leu Thr Ile Leu Arg Met Ala Val
125 130 135
tct cac atg aag tcc ttg agg gga act ggc aac aca tct act gat ggc 605
Ser His Met Lys Ser Leu Arg Gly Thr Gly Asn Thr Ser Thr Asp Gly
140 145 150

```

-continued

tcc tac aag cca tct ttc ctc act gat cag gaa ctg aaa cat ttg atc	653
Ser Tyr Lys Pro Ser Phe Leu Thr Asp Gln Glu Leu Lys His Leu Ile	
155 160 165	
ttg gag gca gca gat ggc ttt ctg ttt att gtc tcc tgt gag act gga	701
Leu Glu Ala Ala Asp Gly Phe Leu Phe Ile Val Ser Cys Glu Thr Gly	
170 175 180	
cgg gtg gtg tat gtc tct gac tca gtg act ccc gtt ttg aac cag cca	749
Arg Val Val Tyr Val Ser Asp Ser Val Thr Pro Val Leu Asn Gln Pro	
185 190 195 200	
cag tct gaa tgg ttc ggg agc aca ctg tat gat cag gtg cac cca gat	797
Gln Ser Glu Trp Phe Gly Ser Thr Leu Tyr Asp Gln Val His Pro Asp	
205 210 215	
gat gtg gat aaa ctt cga gag cag ctc tct aca tca gaa aat gcc cta	845
Asp Val Asp Lys Leu Arg Glu Gln Leu Ser Thr Ser Glu Asn Ala Leu	
220 225 230	
aca ggg cgg gtc ctg gat ctg aag act gga aca gtg aaa aag gaa ggc	893
Thr Gly Arg Val Leu Asp Leu Lys Thr Gly Thr Val Lys Lys Glu Gly	
235 240 245	
cag cag tct tcc atg agg atg tgc atg ggc tca cga agg tcg ttc atc	941
Gln Gln Ser Ser Met Arg Met Cys Met Gly Ser Arg Arg Ser Phe Ile	
250 255 260	
tgc cgc atg agg tgt ggt act agc tcc gtg gac cct gtt tcc atg aat	989
Cys Arg Met Arg Cys Gly Thr Ser Ser Val Asp Pro Val Ser Met Asn	
265 270 275 280	
aga ctg agc ttt ttg agg aac aga tgc agg aat ggg ctt ggc tct gtg	1037
Arg Leu Ser Phe Leu Arg Asn Arg Cys Arg Asn Gly Leu Gly Ser Val	
285 290 295	
aag gaa gga gaa cct cac ttt gtg gta gtc cac tgc aca ggc tac atc	1085
Lys Glu Gly Glu Pro His Phe Val Val Val His Cys Thr Gly Tyr Ile	
300 305 310	
aag gcc tgg cca cca gca ggt gtc tcc ctc cca gat gat gac cca gag	1133
Lys Ala Trp Pro Pro Ala Gly Val Ser Leu Pro Asp Asp Asp Pro Glu	
315 320 325	
gct ggc cag ggg agc aaa ttc tgc cta gtg gcc att ggc agg ctg cag	1181
Ala Gly Gln Gly Ser Lys Phe Cys Leu Val Ala Ile Gly Arg Leu Gln	
330 335 340	
gta act agt tct ccc aac tgt aca gac atg agt aac att tgt cag cca	1229
Val Thr Ser Ser Pro Asn Cys Thr Asp Met Ser Asn Ile Cys Gln Pro	
345 350 355 360	
aca gag ttc atc tcc cga cac aac att gaa ggg ata ttc act ttt gta	1277
Thr Glu Phe Ile Ser Arg His Asn Ile Glu Gly Ile Phe Thr Phe Val	
365 370 375	
gac cat cgt tgt gtg gct act gtt ggc tac cag cca cag gag ctc tta	1325
Asp His Arg Cys Val Ala Thr Val Gly Tyr Gln Pro Gln Glu Leu Leu	
380 385 390	
ggg aag aat att gta gaa ttt tgt cat cct gaa gac caa caa ctt cta	1373
Gly Lys Asn Ile Val Glu Phe Cys His Pro Glu Asp Gln Gln Leu Leu	
395 400 405	
aga gac agc ttt cag cag gtg gtg aaa tta aaa ggt cag gtg ctg tcc	1421
Arg Asp Ser Phe Gln Gln Val Val Lys Leu Lys Gly Gln Val Leu Ser	
410 415 420	
gtc atg ttc cga ttc cga tct aag acc cga gaa tgg ctg tgg atg aga	1469
Val Met Phe Arg Phe Arg Ser Lys Thr Arg Glu Trp Leu Trp Met Arg	
425 430 435 440	
acg agc tcc ttt acc ttc caa aac cct tat tca gat gaa att gag tat	1517
Thr Ser Ser Phe Thr Phe Gln Asn Pro Tyr Ser Asp Glu Ile Glu Tyr	
445 450 455	

-continued

att atc tgc acc aac acc aat gtg aag aac tct agc cag gaa cca cgg Ile Ile Cys Thr Asn Thr Asn Val Lys Asn Ser Ser Gln Glu Pro Arg 460 465 470	1565
cct aca ctg tcc aac acc atc cca agg tca cag cta ggt ccg aca gcc Pro Thr Leu Ser Asn Thr Ile Pro Arg Ser Gln Leu Gly Pro Thr Ala 475 480 485	1613
aat tta tcc cta gag atg ggt aca ggg cag ctg cca tcc agg cag cag Asn Leu Ser Leu Glu Met Gly Thr Gly Gln Leu Pro Ser Arg Gln Gln 490 495 500	1661
cag cag cag cac aca gaa ctg gat atg gta cca gga aga gat ggg ctg Gln Gln Gln His Thr Glu Leu Asp Met Val Pro Gly Arg Asp Gly Leu 505 510 515 520	1709
gcc agc tat aat cat tcc cag gtt tct gtc cag cct gtg gca agt gca Ala Ser Tyr Asn His Ser Gln Val Ser Val Gln Pro Val Ala Ser Ala 525 530 535	1757
gga tca gaa cac agc aag ccc ctt gag aag tca gaa ggt ctc ttt gca Gly Ser Glu His Ser Lys Pro Leu Glu Lys Ser Glu Gly Leu Phe Ala 540 545 550	1805
cag gac aga gat cca agg ttt cca gaa atc tat ccc agc atc act gca Gln Asp Arg Asp Pro Arg Phe Pro Glu Ile Tyr Pro Ser Ile Thr Ala 555 560 565	1853
gat cag agt aaa ggc atc tcc tcc agc act gtc cct gcc acc caa cag Asp Gln Ser Lys Gly Ile Ser Ser Ser Thr Val Pro Ala Thr Gln Gln 570 575 580	1901
ctg ttc tcc cag ggc agc tca ttc cct cct aac ccc cgg ccg gca gag Leu Phe Ser Gln Gly Ser Ser Phe Pro Pro Asn Pro Arg Pro Ala Glu 585 590 595 600	1949
aat ttc agg aat agt ggt ctt acc cct cct gta acc att gtc cag cca Asn Phe Arg Asn Ser Gly Leu Thr Pro Pro Val Thr Ile Val Gln Pro 605 610 615	1997
tca tct tct gca ggg cag ata ctg gcc cag att tca cgt cac tcc aac Ser Ser Ser Ala Gly Gln Ile Leu Ala Gln Ile Ser Arg His Ser Asn 620 625 630	2045
cct gcc cag gga tca gcg ccg acc tgg acc tct agc tcc cgc cca ggc Pro Ala Gln Gly Ser Ala Pro Thr Trp Thr Ser Ser Ser Arg Pro Gly 635 640 645	2093
ttt gcc gcc cag gta gcg cct ctt acc tgt ctg acc ctg tgt gtt gtt Phe Ala Ala Gln Val Ala Pro Leu Thr Cys Leu Thr Leu Cys Val Val 650 655 660	2141
gtt tgt ggg atc ttt ttt ttt tcc tcc agg taa atttattatt gtcagatacc Val Cys Gly Ile Phe Phe Phe Ser Ser Arg 665 670	2194
tccttttcag ttctgtttct tcattctttta attttcatct tttttgcgag gagctagata	2254
attaaaatac cagagataac atccagaagt ctcttttagaa cctatgtttt catatgctca	2314
ccctaagaca gaactgctca ttcacagcag tttgaacagc tttggtctca ggcttggttg	2374
gagtaaatcc aaagagtttg tctttgttta ggactatgta atatagtacc aaagtagaaa	2434
attagtaatt atattcattt atttatgaaa atatagtatc catctatata atatatagta	2494
aatatgttaa atttatttat tactatgtat ttctcttgtc tatataataa tttagaaaag	2554
ttt	2557

<210> SEQ ID NO 101

<211> LENGTH: 4259

<212> TYPE: DNA

<213> ORGANISM: M. musculus

<220> FEATURE:

-continued

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (135) ... (2417)

<400> SEQUENCE: 101

```

gatcttgat tccgcggtag cgggtggcggc ggtaaggtgc ctaatctgcg gactggctct      60
tccctccct cccccagctc ggtggcggtc gccctccca ccgaggggtg cgcagggacg      120
gtgccatctc gacc atg gcg gcg act aca gct aac cca gaa atg aca tca      170
          Met Ala Ala Thr Thr Ala Asn Pro Glu Met Thr Ser
          1                    5                  10
gat gta cca tcg ctg ggt ccc acc att gct tct gga aac cct gga cct      218
Asp Val Pro Ser Leu Gly Pro Thr Ile Ala Ser Gly Asn Pro Gly Pro
          15                    20                  25
ggg att caa ggt gga gga gct gtt gta cag agg gct att aag cga cgg      266
Gly Ile Gln Gly Gly Gly Ala Val Val Gln Arg Ala Ile Lys Arg Arg
          30                    35                  40
tca ggg ctg gat ttt gat gat gaa gta gaa gtg aac act aaa ttt ttg      314
Ser Gly Leu Asp Phe Asp Asp Glu Val Glu Val Asn Thr Lys Phe Leu
          45                    50                  55                  60
aga tgc gat gat gac cag atg tgt aat gac aaa gag cgg ttt gcc agg      362
Arg Cys Asp Asp Asp Gln Met Cys Asn Asp Lys Glu Arg Phe Ala Arg
          65                    70                  75
gaa aat cat agt gaa ata gaa cgg cgg cga cgg aac aag atg aca gct      410
Glu Asn His Ser Glu Ile Glu Arg Arg Arg Asn Lys Met Thr Ala
          80                    85                  90
tac atc aca gaa ctg tca gac atg gta cct aca tgt agt gcc ctg gct      458
Tyr Ile Thr Glu Leu Ser Asp Met Val Pro Thr Cys Ser Ala Leu Ala
          95                    100                  105
cga aaa cca gac aag cta acc atc tta cgc atg gcc gtt tct cac atg      506
Arg Lys Pro Asp Lys Leu Thr Ile Leu Arg Met Ala Val Ser His Met
          110                   115                  120
aag tcc ttg agg gga act ggc aac aca tct act gat ggc tcc tac aag      554
Lys Ser Leu Arg Gly Thr Gly Asn Thr Ser Thr Asp Gly Ser Tyr Lys
          125                   130                  135                  140
cca tct ttc ctc act gat cag gaa ctg aaa cat ttg atc ttg gag gca      602
Pro Ser Phe Leu Thr Asp Gln Glu Leu Lys His Leu Ile Leu Glu Ala
          145                   150                  155
gca gat ggc ttt ctg ttt att gtc tcc tgt gag act gga cgg gtg gtg      650
Ala Asp Gly Phe Leu Phe Ile Val Ser Cys Glu Thr Gly Arg Val Val
          160                   165                  170
tat gtc tct gac tca gtg act ccc gtt ttg aac cag cca cag tct gaa      698
Tyr Val Ser Asp Ser Val Thr Pro Val Leu Asn Gln Pro Gln Ser Glu
          175                   180                  185
tgg ttc ggg agc aca ctg tat gat cag gtg cac cca gat gat gtg gat      746
Trp Phe Gly Ser Thr Leu Tyr Asp Gln Val His Pro Asp Asp Val Asp
          190                   195                  200
aaa ctt cga gag cag ctc tct aca tca gaa aat gcc cta aca ggg cgg      794
Lys Leu Arg Glu Gln Leu Ser Thr Ser Glu Asn Ala Leu Thr Gly Arg
          205                   210                  215                  220
gtc ctg gat ctg aag act gga aca gtg aaa aag gaa ggc cag cag tct      842
Val Leu Asp Leu Lys Thr Gly Thr Val Lys Lys Glu Gly Gln Gln Ser
          225                   230                  235
tcc atg agg atg tgc atg ggc tca cga agg tcg ttc atc tgc cgc atg      890
Ser Met Arg Met Cys Met Gly Ser Arg Arg Ser Phe Ile Cys Arg Met
          240                   245                  250
agg tgt ggt act agc tcc gtg gac cct gtt tcc atg aat aga ctg agc      938
Arg Cys Gly Thr Ser Ser Val Asp Pro Val Ser Met Asn Arg Leu Ser

```

-continued

255	260	265	
ttt ttg agg aac aga tgc agg aat ggg ctt ggc tct gtg aag gaa gga			986
Phe Leu Arg Asn Arg Cys Arg Asn Gly Leu Gly Ser Val Lys Glu Gly			
270	275	280	
gaa cct cac ttt gtg gta gtc cac tgc aca ggc tac atc aag gcc tgg			1034
Glu Pro His Phe Val Val Val His Cys Thr Gly Tyr Ile Lys Ala Trp			
285	290	295	300
cca cca gca ggt gtc tcc ctc cca gat gat gac cca gag gct ggc cag			1082
Pro Pro Ala Gly Val Ser Leu Pro Asp Asp Asp Pro Glu Ala Gly Gln			
305	310	315	
ggg agc aaa ttc tgc cta gtg gcc att ggc agg ctg cag gta act agt			1130
Gly Ser Lys Phe Cys Leu Val Ala Ile Gly Arg Leu Gln Val Thr Ser			
320	325	330	
tct ccc aac tgt aca gac atg agt aac att tgt cag cca aca gag ttc			1178
Ser Pro Asn Cys Thr Asp Met Ser Asn Ile Cys Gln Pro Thr Glu Phe			
335	340	345	
atc tcc cga cac aac att gaa ggg ata ttc act ttt gta gac cat cgt			1226
Ile Ser Arg His Asn Ile Glu Gly Ile Phe Thr Phe Val Asp His Arg			
350	355	360	
tgt gtg gct act gtt ggc tac cag cca cag gag ctc tta ggg aag aat			1274
Cys Val Ala Thr Val Gly Tyr Gln Pro Gln Glu Leu Leu Gly Lys Asn			
365	370	375	380
att gta gaa ttt tgt cat cct gaa gac caa caa ctt cta aga gac agc			1322
Ile Val Glu Phe Cys His Pro Glu Asp Gln Gln Leu Leu Arg Asp Ser			
385	390	395	
ttt cag cag gtg gtg aaa tta aaa ggt cag gtg ctg tcc gtc atg ttc			1370
Phe Gln Gln Val Val Lys Leu Lys Gly Gln Val Leu Ser Val Met Phe			
400	405	410	
cga ttc cga tct aag acc cga gaa tgg ctg tgg atg aga acg agc tcc			1418
Arg Phe Arg Ser Lys Thr Arg Glu Trp Leu Trp Met Arg Thr Ser Ser			
415	420	425	
ttt acc ttc caa aac cct tat tca gat gaa att gag tat att atc tgc			1466
Phe Thr Phe Gln Asn Pro Tyr Ser Asp Glu Ile Glu Tyr Ile Ile Cys			
430	435	440	
acc aac acc aat gtg aag aac tct agc cag gaa cca cgg cct aca ctg			1514
Thr Asn Thr Asn Val Lys Asn Ser Ser Gln Glu Pro Arg Pro Thr Leu			
445	450	455	460
tcc aac acc atc cca agg tca cag cta ggt ccg aca gcc aat tta tcc			1562
Ser Asn Thr Ile Pro Arg Ser Gln Leu Gly Pro Thr Ala Asn Leu Ser			
465	470	475	
cta gag atg ggt aca ggg cag ctg cca tcc agg cag cag cag cag			1610
Leu Glu Met Gly Thr Gly Gln Leu Pro Ser Arg Gln Gln Gln Gln			
480	485	490	
cac aca gaa ctg gat atg gta cca gga aga gat ggg ctg gcc agc tat			1658
His Thr Glu Leu Asp Met Val Pro Gly Arg Asp Gly Leu Ala Ser Tyr			
495	500	505	
aat cat tcc cag gtt tct gtc cag cct gtg gca agt gca gga tca gaa			1706
Asn His Ser Gln Val Ser Val Gln Pro Val Ala Ser Ala Gly Ser Glu			
510	515	520	
cac agc aag ccc ctt gag aag tca gaa ggt ctc ttt gca cag gac aga			1754
His Ser Lys Pro Leu Glu Lys Ser Glu Gly Leu Phe Ala Gln Asp Arg			
525	530	535	540
gat cca agg ttt cca gaa atc tat ccc agc atc act gca gat cag agt			1802
Asp Pro Arg Phe Pro Glu Ile Tyr Pro Ser Ile Thr Ala Asp Gln Ser			
545	550	555	
aaa ggc atc tcc tcc agc act gtc cct gcc acc caa cag ctg ttc tcc			1850
Lys Gly Ile Ser Ser Ser Thr Val Pro Ala Thr Gln Gln Leu Phe Ser			

-continued

560	565	570	
cag ggc agc tca ttc cct cct aac ccc cgg ccg gca gag aat ttc agg Gln Gly Ser Ser Phe Pro Pro Asn Pro Arg Pro Ala Glu Asn Phe Arg 575 580 585			1898
aat agt ggt ctt acc cct cct gta acc att gtc cag cca tca tct tct Asn Ser Gly Leu Thr Pro Pro Val Thr Ile Val Gln Pro Ser Ser Ser 590 595 600			1946
gca ggg cag ata ctg gcc cag att tca cgt cac tcc aac cct gcc cag Ala Gly Gln Ile Leu Ala Gln Ile Ser Arg His Ser Asn Pro Ala Gln 605 610 615 620			1994
gga tca gcg ccg acc tgg acc tct agc tcc cgc cca ggc ttt gcc gcc Gly Ser Ala Pro Thr Trp Thr Ser Ser Ser Arg Pro Gly Phe Ala Ala 625 630 635			2042
cag gtg ccc acc cag gct aca gcc aag act cgt tct tcc caa ttt ggt Gln Val Pro Thr Gln Ala Thr Ala Lys Thr Arg Ser Ser Gln Phe Gly 640 645 650			2090
gtg aac aac ttt cag act tct tcc tcc ttc agt gct atg tct ctt ccg Val Asn Asn Phe Gln Thr Ser Ser Ser Phe Ser Ala Met Ser Leu Pro 655 660 665			2138
ggt gct ccc act gcc tca tct gct cct gag act gga cag acc aca gga Gly Ala Pro Thr Ala Ser Ser Ala Pro Glu Thr Gly Gln Thr Thr Gly 670 675 680			2186
cag ttc cag gcc ccg aca gca gag gcc gtg ggt gtc tgg cca cag tgg Gln Phe Gln Ala Arg Thr Ala Glu Gly Val Gly Val Trp Pro Gln Trp 685 690 695 700			2234
cag ggc cag cag ccc cat cat cgg tct agt tcc agt gag cag cat gtt Gln Gly Gln Gln Pro His His Arg Ser Ser Ser Ser Glu Gln His Val 705 710 715			2282
cag cag aca caa gca caa gca cct agc cag cct gag gtc ttt caa gaa Gln Gln Thr Gln Ala Gln Ala Pro Ser Gln Pro Glu Val Phe Gln Glu 720 725 730			2330
atg ctg tcc atg ctg gga gac caa agc aac acc tac aac aat gaa gaa Met Leu Ser Met Leu Gly Asp Gln Ser Asn Thr Tyr Asn Asn Glu Glu 735 740 745			2378
ttt cct gat cta act atg ttt ccc ccc ttt tcc gaa tag aactattggg Phe Pro Asp Leu Thr Met Phe Pro Pro Phe Ser Glu 750 755 760			2427
gtgagaataa ggggtggggg aaatcactgt ttgtttttaa aagcaaatct tttgtaaaca			2487
gaataaaaagt tcctctccct tcccttcct caccctgat atgtaccctt tccaccctt			2547
gacttgctga agaaacgtta tagaagaaat taaatgaatt tcccaggctt ttaggacct			2607
ctgaaathtt gaggatagggt gaggcctgaa ttcctgtcct tatttcttct gaccagaagt			2667
tgcacagaca tgatttgtgc tggagtcaag gggcagaaca gaagaatctg acaggcacta			2727
attggatact gtggcttgtt tggatagaaa ttctgaatgg agtggaggaa aggagaaatg			2787
ccctcatcac tgaggatcat gaaacacagt aggggtgtgt ggagccttgg gacgtgagca			2847
gtctccagaa agaggcctga gagagagcat gaacacttat ctttgtgagt gagtgagtga			2907
gtgagtgagt gagtgtgtgt gtgtgtgtgt gtgtgtgaga gagagagaga gagagtaaga			2967
gacagagaca gatgggggtga ggggggcatt tgagctccta tgttttgttc cctattatag			3027
agtatatgca aaatttgtcc cagatcttct ttgactttgt gcttgcctct taaagtgtcc			3087
taagaaaatt aattttttca ggtatttttc tatttagtgt tgcagccaaa gagtatttaa			3147
attaagtctt tgctgcactt aaattcatat ccagccaaaa tggaaacttta ggccaacccc			3207

-continued

cagccttctg ttgctagggg tgggtctcta cagacacagt gatcaagctg gatgactcct	3267
gctcttttggg gctttcaact cattgggaag agctgcagat attaccaaaa taggctggct	3327
acatgaacac tgtcagaaat ccagacttg ccacaagga taatgctgca tttttctgtc	3387
agagtcacac atgtttttct ggagaggta tttctgcatg gaaactcaac tcttggatt	3447
agctatcttg agtgaaagtc ctactgacg agtatgcaa ccaaatagcc tcctgcacag	3507
tagcctctcc ttcctgtcac caaacagtt ttaggtctgc tgaagtctgg tgttcttgc	3567
tccttctgca atcttgaaat tggggtttgc tttagagcac aaacataagt ctgtgttagg	3627
tggacttaaa tcccaacagg gtcacttgat aattatagcc atagaaatgc agatgcagg	3687
aactgctttt accctttacc gtcctcagg gagtctcta gatcaacagc cttttttttt	3747
tttttttct taaactggct cctgtcaaag attaagttaa tatggaaaag acctcttatg	3807
tgtattgatg gggcatgagg agcccaggca aggagaggct cgtggagagg ctgaggggat	3867
gttactaagt tccccccgt ttgtctccag tctggtgcca ggcagtagag tggaaaagga	3927
ggctattttt ttattctatg tgcacacata cagtatacat atatatttat atcacatttt	3987
actgaaccaaa aaagtgggt tttccaataa aatacttggt ttttaataac cgacttggtt	4047
ttaactgtga tctgaactat aacgtacagt tattacaggg cttctgaaga agggggggcg	4107
gggagaagct tctctgagg gctcgtctg ctttctctc acggttttat ttttgattgt	4167
tttttcttgt tgccatctg tgctaagcct taactgtggc aaaaataatg acatgtagca	4227
aagattttta aacaaagtat tttttctttt at	4259

<210> SEQ ID NO 102
 <211> LENGTH: 701
 <212> TYPE: DNA
 <213> ORGANISM: M. musculus
 <220> FEATURE:
 <221> NAME/KEY: unsure
 <222> LOCATION: 670
 <223> OTHER INFORMATION: unknown

<400> SEQUENCE: 102

ggaaaccctg gacctgggat tcaaggtgga ggagctgttg tacagagggc tattaagcga	60
cggtcagggc tggattttga tgatgaagta gaagtgaaca ctaaattttt gagatgcgat	120
gatgaccaga tgttttatga caaagagcgg tttgccaggg aaaatcatag tgaaatagaa	180
cggcggcgac ggaacaagat gacagcttac atcacagaac tgtcagacat ggtacctaca	240
tgtagtgtcc tggctcgaaa accagacaag ctaaccatct tacgcatggc cgtttctcac	300
atgaagtcct tgagggaac tggcaacaca tctactgatg gctctacaa gccatcttct	360
ctactgatc aggaactgaa acatttgatc ttggaggcag cagatggctt tctgtttatt	420
gtctctgtg agactggacg ggtgggtgat gtctctgact cagtgactcc cgttttgaac	480
cagccacagt ctgaatggtt cgggagcaca ctgtatgatc aggtgcaccc agatgatgtg	540
gataaacttc gagagcagct ctctacatca gaaaatgcc taacaggtga gagctggctg	600
gacagcagat atgtggggga aaagtcttta tttactcaa gtagttaaga tattttaagc	660
ccgaaaccan aaaaaaaaaa aaaaaaaaaa agggcgccg c	701

<210> SEQ ID NO 103
 <211> LENGTH: 2412
 <212> TYPE: DNA

-continued

```

<213> ORGANISM: M. musculus
<220> FEATURE:
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (120) ... (551)

<400> SEQUENCE: 103

aaaaaaatg cctgaacaga gcaagatgag ataaaaaccc tgtaaaaata tcaactgaata      60
cataggttac ctatgggact ggactaagat gttagtaatt gttcaccttt agtcaatat      119

atg gag ttt att gta ttg agt aat tcc ttg ttt ccc ctt ttg tgt tct      167
Met Glu Phe Ile Val Leu Ser Asn Ser Leu Phe Pro Leu Leu Cys Ser
1          5          10          15

tgt cta ctc tat ttt cct agg aac tct agc cag gaa cca cgg cct aca      215
Cys Leu Leu Tyr Phe Pro Arg Asn Ser Ser Gln Glu Pro Arg Pro Thr
          20          25          30

ctg tcc aac acc atc cca agg tca cag cta ggt ccg aca gcc aat tta      263
Leu Ser Asn Thr Ile Pro Arg Ser Gln Leu Gly Pro Thr Ala Asn Leu
          35          40          45

tcc cta gag atg ggt aca ggg cag ctg cca tcc agg cag cag cag cag      311
Ser Leu Glu Met Gly Thr Gly Gln Leu Pro Ser Arg Gln Gln Gln Gln
          50          55          60

cag cac aca gaa ctg gat atg gta cca aga aga gat ggg ctg gcc agc      359
Gln His Thr Glu Leu Asp Met Val Pro Arg Arg Asp Gly Leu Ala Ser
65          70          75          80

tat aat cat tcc cag gtt tct gtc cag cct gtg gca agt gca gga tca      407
Tyr Asn His Ser Gln Val Ser Val Gln Pro Val Ala Ser Ala Gly Ser
          85          90          95

gaa cac agc aag ccc ctt gag aag tca gaa ggt ctc ttt gca cag gac      455
Glu His Ser Lys Pro Leu Glu Lys Ser Glu Gly Leu Phe Ala Gln Asp
          100          105          110

aga gat cca agg ttt cca gaa atc tat ccc agc atc act gca ggt atg      503
Arg Asp Pro Arg Phe Pro Glu Ile Tyr Pro Ser Ile Thr Ala Gly Met
          115          120          125

ggg ttc ttc cgc agg ctc ctt tta cag gct gag ttt cat tat tac tga      551
Gly Phe Phe Arg Arg Leu Leu Leu Gln Ala Glu Phe His Tyr Tyr
          130          135          140

tgggactgcc cagtcagcat acttctactt cagttacagt acttcatgaa taagtaggaa      611
ttgattaaac tatgtgctac agccccttga tggccctccc ccaactcctt ttggtctgca      671
gatcagagta aaggcatctc ctccagcact gtccctgccca cccaacagct gttctcccag      731
ggcagctcat tccctcctaa cccccggccg gcagagaatt tcaggtgagc cccatatgtg      791
tgtgtgtgctt gacagggttc tgcagggttc agttgtctgga tccgtgtgtc atcttccctt      851
gttttctctg gtcacctcag acaaagcagt agaacttact ggacctaggg tgagacaacg      911
aagctgcttt tcctcctgtt ttgtcaccta ttctattgcc ttgctctagg ttccaaacgt      971
ctctgtgtgg tcagtgtgtg acagtcagtc tttcttgtgt ttttaaatat atcagggttt      1031
ccttaactcc aagaaatcag aggaatctag ggatagaatg tgtcctttga ttcatagctt      1091
ctgtgatgga gtcaaccttt taaccttcac tttctatttg ttctctccta ggaatagtgg      1151
tcttaccctt cctgtaacca ttgtccagcc atcatcttct gcagggcaga tactggccca      1211
gatttcacgt cactccaacc ctgccagggt atcagcgccg acctggacct ctagctcccg      1271
cccaggtttt gccgcccagg tagcgctctt tacctgtctg accctgtgtg ttgttggttg      1331
tgggatcttt ttttttccct ccaggtaaat ttattattgt cagatacctc cttttcagtt      1391

```

-continued

cctgttcttc atcttttaaat tttcatcttt ttgtcgagga gctagataat taaaatacca	1451
gagataacat ccagaagtct ctttagaacc tatgttttca tatgctcacc ttaagacaga	1511
actgctcatt cacagcagtt tgaacagctt tggctctcagg cttgtttgga gtaaatccaa	1571
agagtgtgtc ttgttttagg actatgtaat atagtaccaa agtagaaaat tagtaattat	1631
attcatttat ttatgaaaat atagtatcca tctatataat atatagtaaa tatgttaaat	1691
ttatttatta ctatgtattt ctcttgtcta tataataatt tagaaaagtt taaaaaaaaa	1751
tgaaaactca aacttgactc cagaattggt ctctatagct tttttgtgta tgtgtaaaaa	1811
tactcaggaa tgttgcccat gactcttggt caggatgtgc cgtgatgttg atgacagctg	1871
ctaccatggt ttctacatcg gtgacataat caagcatgca tatattatct cccttggagt	1931
tactttttaa attgtggatt taaaacggtc tctagaaatt attgtatctc acaaaaaatg	1991
ttagaggcaa taactagttt cttaatcaat atacagtaaa tgggtgtgag aaaggacagc	2051
tttaatttca acaaagagac tgaggcagga gcatgggcct gggccacata gtgagagata	2111
aactgtctca taaaagaaag aacagaacaa aaccaaata gcataatgga aaataaaaga	2171
ggacattgtc cactgtgcca agtaacagtc tcttctgggtg gggttaacag tgaggtttca	2231
tttctagttt attttttcca atttttttct attctttttg aggagatctt agaatttata	2291
ttaaacaacc ctttgcagat ttacacttaa agtcaagagc aaaagagaag cactcagaac	2351
tgagtgtggg tgtgaactcc ctaagatgcc accaaattcc tctgtaacac atagggattc	2411
c	2412

<210> SEQ ID NO 104
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 104

gattccagca gaaacaagat	20
-----------------------	----

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

<400> SEQUENCE: 105

agtaccataa ccaggaagag	20
-----------------------	----

<210> SEQ ID NO 106
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 106

atcatcgcat ctgaaaagaa	20
-----------------------	----

<210> SEQ ID NO 107
 <211> LENGTH: 20
 <212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 107

tcatacttgctgctgcagcctg 20

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

<400> SEQUENCE: 108

agattaggca ccttaccgcc 20

<210> SEQ ID NO 109
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 109

gccgccatgg tcgagatggc 20

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

<400> SEQUENCE: 110

gttagctgta gtcgccgccca 20

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

<400> SEQUENCE: 111

tcattttctgg gttagctgta 20

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

<400> SEQUENCE: 112

acatctgatg tcattttctgg 20

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

-continued

<400> SEQUENCE: 113

ttccagaagc aatggtggga

20

<210> SEQ ID NO 114

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 114

agctcctcca ccttgaatcc

20

<210> SEQ ID NO 115

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 115

cgtcgcttaa tagccctctg

20

<210> SEQ ID NO 116

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 116

cagccctgac cgtcgcttaa

20

<210> SEQ ID NO 117

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 117

catcaaaatc cagccctgac

20

<210> SEQ ID NO 118

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 118

ctggcaaacc gctctttgtc

20

<210> SEQ ID NO 119

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 119

atcatccgac ctggcaaacc

20

-continued

<210> SEQ ID NO 120
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 120

agctctgctc atcatccgac

20

<210> SEQ ID NO 121
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 121

gtctctcttt atccgcagag

20

<210> SEQ ID NO 122
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 122

ctggcaagtc tctctttatc

20

<210> SEQ ID NO 123
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 123

tttccctggc aagtctctct

20

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

<400> SEQUENCE: 124

atgattttcc ctggcaagtc

20

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

<400> SEQUENCE: 125

gtaagctgtc atcttggtcc

20

<210> SEQ ID NO 126
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 126

gttctgtgat gtaagctgtc 20

<210> SEQ ID NO 127
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 127

tagcttgtct gggtttcgag 20

<210> SEQ ID NO 128
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 128

caaatgtttc agttcctgat 20

<210> SEQ ID NO 129
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 129

taaacagaaa gccatctgct 20

<210> SEQ ID NO 130
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 130

tggttcaaaa cgggagtcac 20

<210> SEQ ID NO 131
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 131

gctgctctcg aagtttatcc 20

<210> SEQ ID NO 132
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 132

gcacatcctc atggaagact

20

<210> SEQ ID NO 133

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 133

ttcatggaaa cagggtccac

20

<210> SEQ ID NO 134

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 134

gctcagtcta ttcatggaaa

20

<210> SEQ ID NO 135

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 135

tcctcaaaaa gctcagtcta

20

<210> SEQ ID NO 136

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 136

ctgcatctgt tcctcaaaaa

20

<210> SEQ ID NO 137

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 137

tgcagtgga caccacaaag

20

<210> SEQ ID NO 138

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 138

ggccagcctc tgggtcatca

20

-continued

<210> SEQ ID NO 139
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 139

cagaatttgc tccccctggcc 20

<210> SEQ ID NO 140
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 140

ggccactagg cagaatttgc 20

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

<400> SEQUENCE: 141

cagcctgccca atggccacta 20

<210> SEQ ID NO 142
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 142

gtgaatatcc cttcaatgtt 20

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

<400> SEQUENCE: 143

acagtagcca cacaacgatg 20

<210> SEQ ID NO 144
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 144

gacaaaattc tacaatatcc 20

<210> SEQ ID NO 145
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 145

gtcttcagga tgacaaaatt 20

<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 146

gaagttgttg gtcttcagga 20

<210> SEQ ID NO 147
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 147

gctgtctctt agaagttggt 20

<210> SEQ ID NO 148
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 148

cctgctgaaa gctgtctctt 20

<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 149

aatttcacca cctgctgaaa 20

<210> SEQ ID NO 150
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 150

tcattccacag ccattctcgg 20

<210> SEQ ID NO 151
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 151

gtgggttcctg gctagagttc

20

<210> SEQ ID NO 152

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 152

gtcggaccta gctgtgacct

20

<210> SEQ ID NO 153

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 153

ctgtacccat ctctagggat

20

<210> SEQ ID NO 154

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 154

ccagcccatc tcttcctggt

20

<210> SEQ ID NO 155

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 155

ggacagaaac ctgggaatga

20

<210> SEQ ID NO 156

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 156

gggcttgctg tggtctgac

20

<210> SEQ ID NO 157

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 157

aagagacctt ctgacttctc

20

-continued

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

<400> SEQUENCE: 158

cctgggagaa cagctgttgg 20

<210> SEQ ID NO 159
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 159

aatgagctgc cctgggagaa 20

<210> SEQ ID NO 160
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 160

gttaggaggg aatgagctgc 20

<210> SEQ ID NO 161
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 161

cactattcct gaaattctct 20

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

<400> SEQUENCE: 162

atctgcctg cagaagatga 20

<210> SEQ ID NO 163
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 163

aagaacgagt cttggtgta 20

<210> SEQ ID NO 164
<211> LENGTH: 20
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 164
tctgaaagtt gttcacacca 20

<210> SEQ ID NO 165
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 165
gtctcaggag gaaagttgga 20

<210> SEQ ID NO 166
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 166
cctgccactg tggccagaca 20

<210> SEQ ID NO 167
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 167
ttcttgaaag acctcaggct 20

<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 168
tctcccagca tggacagcat 20

<210> SEQ ID NO 169
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 169
ccaatagttc tattcgaaa 20

<210> SEQ ID NO 170
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 170

tctgtttaca aaagatttgc

20

<210> SEQ ID NO 171

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 171

cggaatccaa gatggcggac

20

<210> SEQ ID NO 172

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 172

ctccaaacaa gcctgagacc

20

<210> SEQ ID NO 173

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 173

atgattttcc ctggcaaacc

20

<210> SEQ ID NO 174

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 174

ggcacctggg cggcaaagcc

20

<210> SEQ ID NO 175

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 175

agactttttcc cccacatatc

20

<210> SEQ ID NO 176

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 176

taacctatgt attcagtgat

20

-continued

<210> SEQ ID NO 177
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 177

ttcgcgggctg gacgattcag 20

<210> SEQ ID NO 178
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 178

cctggcaaca tctgggggttg g 21

<210> SEQ ID NO 179
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 179

caacaggctg gagtgactgg gctcc 25

<210> SEQ ID NO 180
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 180

gtggagacag gactagtgc cgaatg 26

<210> SEQ ID NO 181
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 181

ctgtggaggc atggactgag aatgg 25

<210> SEQ ID NO 182
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 182

ctgggaacct ccaaattccc tggc 24

<210> SEQ ID NO 183
<211> LENGTH: 26
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 183

ctgggcaggg ttggcagctg ccttac 26

<210> SEQ ID NO 184
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 184

tgagctgtct gtgatccagc 20

<210> SEQ ID NO 185
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 185

gcgctgctcc caagaactct 20

<210> SEQ ID NO 186
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 186

tcctcatggt cacatggatg 20

<210> SEQ ID NO 187
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 187

cgagaggcgg acgggaccg 19

<210> SEQ ID NO 188
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 188

cgagaggcgg acgggaccgt t 21

<210> SEQ ID NO 189
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Compound

-continued

<400> SEQUENCE: 189

ttgctctccg cctgccctgg c

21

<210> SEQ ID NO 190

<211> LENGTH: 19

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antisense Compound

<400> SEQUENCE: 190

gctctccggc tgccctggc

19

What is claimed:

1. An antisense oligonucleotide 13 to 50 nucleobases in length which is specifically hybridizable with a nucleic acid molecule encoding human HIF1-beta, said antisense oligonucleotide comprising at least one modification selected from the group consisting of a modified internucleoside linkage, a modified sugar moiety and a modified nucleobase, wherein said antisense oligonucleotide inhibits expression of human HIF1-beta.

2. The antisense oligonucleotide of claim 1 comprising 13 to 30 nucleobases in length.

3. The antisense oligonucleotide of claim 1, wherein the modified internucleoside linkage is a phosphorothioate linkage.

4. The antisense oligonucleotide of claim 1, wherein the modified sugar moiety is a 2'-O-(2-methoxyethyl) moiety.

5. The antisense oligonucleotide of claim 1, wherein the modified nucleobase is a 5-methyl cytosine.

6. The antisense oligonucleotide of claim 1 which is a chimeric oligonucleotide.

7. The chimeric antisense oligonucleotide of claim 6 having a first region comprising 2'-deoxynucleotides and second and third regions flanking said first region, comprising at least one 2'-O-(2-methoxyethyl) nucleotide.

8. The chimeric antisense oligonucleotide of claim 7, wherein said first region is ten 2'-deoxynucleotides in length and said second and third regions are each five nucleotides in length.

9. The chimeric antisense oligonucleotide of claim 8 further comprising a phosphorothioate internucleoside linkage at each position.

10. A pharmaceutical composition comprising the antisense oligonucleotide of claim 1 and a pharmaceutically acceptable carrier or diluent.

11. A method of inhibiting expression of human HIF1-beta in cells or tissues, comprising contacting said cells or tissues

with the antisense oligonucleotide of claim 1, such that expression of human HIF1-beta is inhibited.

12. A method of inhibiting expression of a HIF1-beta regulated gene in a cell or tissue comprising contacting said cells or tissues with the antisense oligonucleotide of claim 1, such that expression of the HIF1-beta regulated gene is inhibited.

13. The method of claim 12, wherein the HIF1-beta regulated gene is selected from the group consisting of VEGF, GLUT-1, PGK-1, PAI-1 and Epo.

14. A method of treating an animal having a disease or condition associated with HIF1-beta comprising administering to said animal a therapeutically or prophylactically effective amount of the composition of claim 10 so that expression of HIF1-beta is inhibited.

15. The method of claim 14, wherein the disease or condition is a hyperproliferative disorder.

16. The method of claim 15, wherein the hyperproliferative disorder is cancer.

17. The method of claim 15, wherein the hyperproliferative disorder is an angiogenic disorder.

18. The method of claim 17, wherein the angiogenic disorder is an ocular disorder.

19. The method of claim 18, wherein the ocular disorder is selected from the group consisting of macular degeneration, diabetic retinopathy, macular edema and retinopathy of prematurity.

20. A method of preventing or inhibiting aberrant angiogenesis in an animal, comprising administering to said animal an antisense oligonucleotide of claim 1 such that aberrant angiogenesis is prevented or inhibited.

* * * * *