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(54) Title: MODULATION OF HIF1-BETA EXPRESSION

(57) Abstract: Compounds, compositions and methods are provided for modulating the expression of HIF 1-beta. The compositions comprise oligonucleotides, targeted to nucleic acid encoding HIF1-beta. Methods of using these compounds for modulation of HIF1-beta expression and for diagnosis and treatment of diseases and conditions associated with expression of HIF1-beta are provided.



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MODULATION OF HIF1-BETA EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of priority to U.S. provisional patent application Serial No. 60/604,190, filed August 25, 2004, and U.S. provisional patent application Serial No. 60/649,586, filed February 2, 2005, both of which are incorporated herein by reference in their entirety.

10 FIELD OF THE INVENTION

 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
15 of HIF1-beta.

BACKGROUND OF THE INVENTION

 Oxygen homeostasis in mammals is tightly regulated, necessitated by the need to maintain sufficient levels for critical oxygen-dependent processes while minimizing the
20 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.
25 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
30 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).

 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

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hypoxia-responsive element (HRE) in the 3' enhancer of the erythropoietin gene (Wang and Semenza, *Proc Natl Acad Sci U S A*, **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 U S A*, **2000**, 97, 10436-10441).

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 U S A*, **1993**, 90, 4304-4308); (Maxwell et al., *Proc Natl Acad Sci U S A*, **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 (Rolfs 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

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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).

5 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
10 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).
15 Binding of the heterodimer to the HRE induces gene expression (Wiesener et al., *Blood*, **1998**, 92, 2260-2268).

 In contrast to the HIF-alpha subunits, HIF1-beta 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
20 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-
25 binding and nuclear translocation, AHR forms a dimer with HIF1-beta, resulting in the activation of a number of genes involved in drug metabolism, such as the cytochromes P450, CYP1A1, CYP1A2, and CYP1B1. AHR/HIF1-beta 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,
30 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-beta heterodimer directly associates with the estrogen receptors ER-alpha and ER-beta. They showed that this association

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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.

The role of HIF1-beta 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-beta 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).

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

U.S. Patent 6,352,829 discloses the use of an oligonucleotide 26 nucleotides in length as a PCR primer for amplification of the HIF1-beta sequence.

U.S. pre-grant publication 2004-0152655 discloses antisense oligonucleotide compounds for inhibiting HIF1-alpha.

U.S. pre-grant publication 2004-0096848 discloses oligomeric compounds directed against HIF1-alpha.

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

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

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

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-alpha.

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-alpha, HIF2-alpha or HIF3-alpha.

Currently, there are no known therapeutic agents which effectively inhibit the synthesis of HIF1-beta and to date, investigative strategies aimed at modulating the function of HIF1-beta

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have involved the use of antibodies and inactive mutants. Consequently, there remains a long felt need for additional agents capable of effectively inhibiting HIF1-beta function.

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-beta expression. Provided herein are antisense compounds for inhibition of HIF1-beta expression. The disclosed compounds can be used for treating or preventing conditions associated with HIF1-beta, such as cancer and angiogenic disorders.

SUMMARY OF THE INVENTION

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-beta, and which modulate the expression of HIF1-beta. 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-beta are also set forth herein.

Provided herein are antisense oligonucleotides which are specifically hybridizable with a nucleic acid molecule encoding human HIF1-beta. The HIF1-beta 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-beta antisense oligonucleotides further comprise a complementary strand. Also provided are antisense oligonucleotides which specifically hybridize to a splice variant of human HIF1-beta.

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-beta. 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.

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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.

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.

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.

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.

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 or 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

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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.

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 therapeutically 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.

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.

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 THE INVENTION

A. Overview of the Invention

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.

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

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.

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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
5 in the art will be able to determine when an oligomeric compound is specifically hybridizable.

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

The present invention employs antisense compounds, preferably oligonucleotides and similar species for use in modulating the function or effect of nucleic acid molecules encoding
10 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
15 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,
20 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.

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
25 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
30 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.

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.

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.

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.

"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

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.

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.

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.

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. Nonlimiting

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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-
5 stranded, circular, branched or hairpins 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.

The oligomeric compounds in accordance with this invention comprise compounds from
10 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.

15 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.

20 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.

In one embodiment, the antisense compounds of the invention comprise 13 to 30
25 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.

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.

30 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.

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

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

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

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

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

5 In one embodiment, the antisense compounds of the invention comprise 15 nucleobases.

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

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

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

10 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.

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.

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

30

C. Targets of the Invention

"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

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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.

5 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
10 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.

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,
15 introns, intron-exon junctions and exon-exon junctions.

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
20 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
25 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
30 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

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adjacent to the cap site.

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.

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.

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.

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.

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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
5 believed that these target segments represent portions of the target nucleic acid which are accessible for hybridization.

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.

10 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
15 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
20 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.

25 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.

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

30 **D. Kits, Research Reagents, Diagnostics, and Therapeutics**

The antisense compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. Furthermore, antisense

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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.

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.

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.

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).

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

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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
5 for detecting the level of HIF1-beta in a sample may also be prepared.

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
10 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.

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
15 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
20 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
25 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%.

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
30 encoding HIF1-beta protein and/or the HIF1-beta protein itself.

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

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)

Specific examples of oligomeric antisense compounds useful in this invention include oligonucleotides containing 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.

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-

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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
5 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.

10 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).

15 Representative United States patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S.: 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;
20 5,527,899; 5,721,218; 5,672,697 and 5,625,050, each of which is herein incorporated by reference.

In some embodiments of the invention, oligomeric compounds may have one or more phosphorothioate and/or heteroatom internucleoside linkages, in particular -CH₂-NH-O-CH₂-, -CH₂-N(CH₃)-O-CH₂- (known as a methylene (methylimino) or MMI backbone), -CH₂-O-
25 N(CH₃)-CH₂-, -CH₂-N(CH₃)-N(CH₃)-CH₂- and -O-N(CH₃)-CH₂-CH₂- (wherein the native phosphodiester internucleotide linkage is represented as -O-P(=O)(OH)-O-CH₂-). The MMI type internucleoside linkages are disclosed in the above referenced U.S. patent 5,489,677. Amide internucleoside linkages are disclosed in the above referenced U.S. patent 5,602,240.

Some oligonucleotide backbones that do not include a phosphorus atom therein have
30 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,

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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 CH₂ component parts.

Representative United States patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S.: 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)

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.

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 (-C(=O)-CH₂- 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.: 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, CA, 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

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termini. In particular, 1-8 lysine or arginine residues are useful when conjugated to the end of a PNA molecule.

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 United States Patent 5,034,506, issued July 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. US Patent 5,166,315 discloses linkages including -O-P(=O)(N(CH₃)₂)-O-; US Patent 5,034,506 discloses achiral intermorpholino linkages; and US Patent 5,185,444 discloses phosphorus containing chiral intermorpholino linkages.

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

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sequence targeting RNA was stable to serum and able to activate E. coli RNase resulting in cleavage of the target RNA strand.

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 Invens. 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. Patents: 6,268,490 and 6,670,461). The linkage can be a methylene (-CH₂-) 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, CO, USA).

An isomer of LNA that has also been studied is α -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 α -L-LNA's were incorporated into antisense gapmers and chimeras that showed potent antisense activity.

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. Patent 6,043,060).

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).

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-

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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.

LNAs also form duplexes with complementary DNA, RNA or LNA with high thermal
5 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
10 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).

Potent and nontoxic antisense oligonucleotides containing LNAs have been described
15 (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
20 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 LNA's 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
25 RNA polymerase II (Fluiter *et al.*, *Nucleic Acids Res.*, **2003**, *31*, 953-962).

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.

The first analogs of LNA, phosphorothioate-LNA and 2'-thio-LNAs, have also been
30 prepared (Kumar *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222). Preparation of locked nucleoside analogs containing oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel *et al.*, WO 99/14226). Furthermore, synthesis of

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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.

5 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')- α -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
10 template (reported in C&EN/January 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).

In one study (3',2')- α -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
15 shown to bind to RNA and DNA with comparable strength to that of RNA/DNA.

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
20 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.

25 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
30 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

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.

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.: 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.

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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.

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 Figure 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

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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.)

5 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
10 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.)

 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
15 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, NY.; Lesnik et al., *Biochemistry*, 1995, 34, 10807-10815; Conte et al., *Nucleic Acids Res.*, 1997, 25,
20 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
25 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, NY). As used herein, B-form geometry is inclusive of both C2'-endo pucker and
30 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,

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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.

One routinely used method of modifying the sugar puckering 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 puckering 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.

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 ¹H NMR 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

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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.

5 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
10 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.

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'-O-substituted alkyl and 2'-fluoro substituent groups. Suitable for the substituent groups are various alkyl and
15 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 internucleoside linkages to enhance properties such as but not limited to activity in a selected application.

20 *Natural and Modified Nucleobases*

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),
25 and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-
30 CH₃) 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-

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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), pyridoinindole cytidine (H-pyrido[3',2':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-deazaguanosine, 2-aminopyridine and 2-pyridone.

Further nucleobases include those disclosed in United States Patent 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.

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. 3,687,808, as well as U.S.: 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 United States patent 5,750,692, which is commonly owned with the instant application and also herein incorporated by reference.

Conjugates

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

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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 cholesterols, 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 October 23, 1992, and U.S. Patent 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-glycerol-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-triiodobenzoic acid, flufenamic acid, folic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in United States Patent Application 09/334,130 (filed June 15, 1999) which is incorporated herein by reference in its entirety.

Representative United States patents that teach the preparation of such oligonucleotide conjugates include, but are not limited to, U.S.: 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;

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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
5 incorporated by reference.

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
10 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
15 (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-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide;
20 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
25 herein).

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;
30 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; threo-pentofuransyl 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;

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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).

5 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 January 16, 2003.

Chimeric compounds

10 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.

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.

30 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

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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').

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.

Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S.: 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

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.: 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.

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.

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 December 9, 1993 or in WO 94/26764 and U.S. 5,770,713 to Imbach *et al.*

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. Patent 6,287,860, which is incorporated herein in its entirety.

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

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(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.

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.

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.

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.

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. Patent 6,287,860, which is incorporated herein in its entirety.

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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. Patent 6,287,860, which is incorporated herein in its entirety.

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

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

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.

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

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The following compounds, including amidites and their intermediates were prepared as described in US Patent 6,426,220 and published PCT WO 02/36743; 5'-O-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-methylcytidine 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-(dimethylaminooxyethyl) nucleoside amidites, 2'-(Dimethylaminooxyethoxy) nucleoside amidites, 5'-O-*tert*-Butyldiphenylsilyl-O²-2'-anhydro-5-methyluridine, 5'-O-*tert*-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine, 2'-O-([2-phthalimidooxy)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* dimethylaminooxyethyl]-5-methyluridine, 2'-O-(dimethylaminooxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(dimethylaminooxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(2-*N,N*-dimethylaminooxyethyl)-5-methyluridine-3'-[(2-cyanoethyl)-*N,N*-diisopropylphosphoramidite], 2'-(Aminooxyethoxy) nucleoside amidites, N²-isobutyryl-6-O-diphenylcarbamoyl-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*-dimethylaminoethoxy)-ethyl]-5-methyl uridine and 5'-O-

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

Example 2

5 Oligonucleotide and oligonucleoside synthesis

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, CA). Any other means for such synthesis known in the art may additionally or
10 alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives.

Oligonucleotides

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

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-2H-benzodithiole-3-one 1,1-dioxide in acetonitrile for the oxidation of the phosphite linkages. The
20 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. Patent 5,508,270, herein incorporated by reference.

25 Alkyl phosphonate oligonucleotides are prepared as described in U.S. Patent 4,469,863, herein incorporated by reference.

3'-Deoxy-3'-methylene phosphonate oligonucleotides are prepared as described in U.S. Patents 5,610,289 or 5,625,050, herein incorporated by reference.

Phosphoramidite oligonucleotides are prepared as described in U.S. Patent, 5,256,775 or
30 U.S. Patent 5,366,878, herein incorporated by reference.

Alkylphosphorothioate 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.

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3'-Deoxy-3'-amino phosphoramidate oligonucleotides are prepared as described in U.S. Patent 5,476,925, herein incorporated by reference.

Phosphotriester oligonucleotides are prepared as described in U.S. Patent 5,023,243, herein incorporated by reference.

5 Borano phosphate oligonucleotides are prepared as described in U.S. Patents 5,130,302 and 5,177,198, both herein incorporated by reference.

Oligonucleosides

Methylenemethylimino linked oligonucleosides, also identified as MMI linked
10 oligonucleosides, methylenedimethylhydrazo 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. Patents
15 5,378,825, 5,386,023, 5,489,677, 5,602,240 and 5,610,289, all of which are herein incorporated by reference.

Formacetal and thioformacetal linked oligonucleosides are prepared as described in U.S. Patents 5,264,562 and 5,264,564, herein incorporated by reference.

Ethylene oxide linked oligonucleosides are prepared as described in U.S. Patent
20 5,223,618, herein incorporated by reference.

Example 3

RNA Synthesis

In general, RNA synthesis chemistry is based on the selective incorporation of various
25 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
30 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.

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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.

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.

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 (S_2Na_2) 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.

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, CO), 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.

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,

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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.,
5 *Tetrahedron*, **1967**, *23*, 2301-2313; Griffin, B. E., et al., *Tetrahedron*, **1967**, *23*, 2315-2331).

RNA antisense compounds (RNA oligonucleotides) of the present invention can be synthesized by the methods herein or purchased from Dharmacon Research, Inc (Lafayette, CO). 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,
10 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 5X 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
15 acid, or for diagnostic or therapeutic purposes.

Example 4

Synthesis of Chimeric Compounds

Chimeric oligonucleotides, oligonucleosides or mixed oligonucleotides/oligonucleosides
20 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
25 are also known in the art as "hemimers" or "wingmers".

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

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
30 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

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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

[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

[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.

Other chimeric oligonucleotides, chimeric oligonucleosides and mixed chimeric oligonucleotides/oligonucleosides are synthesized according to United States patent 5,623,065, herein incorporated by reference.

Example 5

Design and screening of duplexed antisense compounds targeting HIF1-beta

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

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

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:

```

      cgagaggcggacgggaccgTT  Antisense Strand  (SEQ ID NO: 188)
      |||||
10  TTgctctccgcctgccctggc    Sense Strand      (SEQ ID NO: 189)

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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.

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:

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      cgagaggcggacgggaccg    Antisense Strand  (SEQ ID NO: 187)
      |||||
20  gctctccgcctgccctggc     Sense Strand      (SEQ ID NO: 190)

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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.

RNA strands of the duplex can be synthesized by methods disclosed herein or purchased from Dharmacon Research Inc., (Lafayette, CO). 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 5X solution of annealing buffer. The final concentration of said buffer is 100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, and 2mM 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.

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

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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

10 Oligonucleotide Isolation

After cleavage from the controlled pore glass solid support and deblocking in concentrated ammonium hydroxide 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

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 sulfurization 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, CA, or Pharmacia, Piscataway, NJ). Non-standard nucleosides are synthesized as per standard or patented methods. They are utilized as base protected beta-cyanoethyldiisopropyl phosphoramidites.

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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.

5

Example 8**Oligonucleotide Analysis – 96-Well Plate Format**

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
10 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
15 acceptable if at least 85% of the compounds on the plate were at least 85% full length.

Example 9**Cell culture and oligonucleotide treatment**

The effect of antisense compounds on target nucleic acid expression can be tested in any
20 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
25 protection assays, or RT-PCR.

T-24 cells:

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, CA) supplemented
30 with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, CA), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, CA). 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

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for use in RT-PCR analysis.

A549 cells:

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, CA) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, CA), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, CA). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence.

NHDF cells:

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.

HEK cells:

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.

b.END cells:

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, CA) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, CA). 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.

MCF7 cells:

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, CA). 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.

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PC3 cells:

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, CA) and antibiotics (Invitrogen Life Technologies, Carlsbad, CA). 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.

Hep3B cells:

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, CA). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence.

HeLa cells:

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, CA) supplemented with 10% fetal bovine serum (Invitrogen Corporation, Carlsbad, CA). 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.

HuVEC cells:

The human umbilical vein endothelial cell line HuVEC is obtained from Cascade Biologics (Portland, OR). HuVEC cells are routinely cultured in EBM (Clonetics Corporation Walkersville, MD) supplemented with SingleQuots supplements (Clonetics Corporation,

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Walkersville, MD). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence and are maintained for up to 15 passages.

Treatment with antisense compounds:

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, CA) and then treated with 130 μ L of OPTI-MEM™-1 containing 3.75 μ g/mL LIPOFECTIN™ (Invitrogen Corporation, Carlsbad, CA) 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.

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 (TCCGTCATCGCTCCTCAGGG, SEQ ID NO: 1) which is targeted to human H-ras, or ISIS 18078, (GTGCGCGCGAGCCCGAAATC, 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 (ATGCATTCTGCCCAAGGA, SEQ ID NO: 3), a 2'-O-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.

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.

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Example 10**Analysis of oligonucleotide inhibition of HIF1-beta expression**

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, CA and used according to manufacturer's instructions.

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, Birmingham, MI), 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*

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. 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, OR; PerkinElmer, Boston, MA), protein-based assays including enzymatic assays (Panvera, LLC, Madison, WI; BD Biosciences, Franklin Lakes, NJ; Oncogene Research Products, San Diego, CA), cell regulation, signal transduction, inflammation, oxidative processes and apoptosis (Assay Designs Inc., Ann Arbor, MI), triglyceride accumulation

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(Sigma-Aldrich, St. Louis, MO), angiogenesis assays, tube formation assays, cytokine and hormone assays and metabolic assays (Chemicon International Inc., Temecula, CA; Amersham Biosciences, Piscataway, NJ).

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.

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.

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

Poly(A)+ mRNA isolation

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 CA). 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.

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

Total RNA Isolation

5 Total RNA was isolated using an RNEASY 96™ kit and buffers purchased from Qiagen Inc. (Valencia, CA) 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 µL cold PBS. 150 µL Buffer RLT was added to each well and the plate vigorously agitated for 20 seconds. 150 µL of 70% ethanol was then added to each well and the contents
10 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 µL 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 µL of Buffer RW1 was added to
15 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
20 collection tube rack containing 1.2 mL collection tubes. RNA was then eluted by pipetting 140 µL of RNase free water into each well, incubating 1 minute, and then applying the vacuum for 3 minutes.

 The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia CA). Essentially, after lysing of the cells on the culture plate, the
25 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

30 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, CA) according to manufacturer's instructions. This is a closed-tube,

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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, CA, Operon Technologies Inc., Alameda, CA or Integrated DNA Technologies Inc., Coralville, IA) is attached to the 5' end of the probe and a quencher dye (e.g., TAMRA, obtained from either PE-Applied Biosystems, Foster City, CA, Operon Technologies Inc., Alameda, CA or Integrated DNA Technologies Inc., Coralville, IA) 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.

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.

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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, CA). RT, real-time PCR reactions were carried out by adding 20 μ L PCR cocktail (2.5x 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 2.5x 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.

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, OR). 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, OR). Methods of RNA quantification by RiboGreen™ are taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374).

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

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: TGGCGTTGTTGAACATGTT (SEQ ID NO: 6) and the PCR probe was: FAM-CCAGCAGCCTCATCATCGTTCA-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: GAAGGTGAAGGTCGGAGTC (SEQ ID NO: 8)

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

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: GGTAAGACCACTATTCCTGAAATTCTCT (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: GGCAAATTCAACGGCACAGT (SEQ ID NO: 15)

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

Eighteen hours after antisense treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL™ (TEL-TEST "B" Inc., Friendswood, TX). 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 (AMRESCO, Inc. Solon, OH). RNA was transferred from the gel to HYBOND™-N+ nylon membranes (Amersham Pharmacia Biotech, Piscataway, NJ) by overnight capillary transfer using a Northern/Southern Transfer buffer system (TEL-TEST "B" Inc., Friendswood, TX). RNA transfer was confirmed by UV visualization. Membranes were fixed by UV cross-linking using a STRATALINKER™ UV Crosslinker 2400 (Stratagene, Inc, La Jolla, CA) and then probed using QUICKHYB™ hybridization solution (Stratagene, La Jolla, CA) using manufacturer's recommendations for stringent conditions.

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-

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3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, CA).

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 GGTAAGACCACTATTCTGAAATTCTCT (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, CA).

Hybridized membranes were visualized and quantitated using a PHOSPHORIMAGER™ and IMAGEQUANT™ Software V3.3 (Molecular Dynamics, Sunnyvale, CA). 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

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'-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 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 100nM 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".

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Table 1
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 SITE	SEQUENCE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
311073	Intron 1	18	1578	acacacatatctcaaggccc	65	21	2
311074	Intron 1	18	10523	aaggagcagaggactccct	6	22	2
311075	Intron 1	18	15791	caagatcaggctgggaaca	25	23	2
311076	Intron 2	18	23071	cccctaactctggcacctgt	71	24	2
311077	Intron 8: Exon 9 junction	18	44694	actgccacacctgtttcaag	51	25	2
311078	Intron 13	18	52827	taggaataataactatttc	0	26	2
311079	Exon 21: Intron 21 junction	18	63922	actctctacctggaagacc	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	tccgacctggcaaaccgctc	52	34	2
311087	Coding	4	393	catcatccgacctggcaaac	17	35	2
311088	Coding	4	432	atttccctggcaagtctct	55	36	2
311089	Coding	4	472	ctgtcatctgttcgctgc	69	37	2
311090	Coding	4	494	tctgacagtctgtgatgta	82	38	2
311091	Coding	4	527	tttcgagccagggcactaca	83	39	2
311092	Coding	4	532	ctggtttcgagccagggca	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	aaagccatctgctgcctcca	80	46	2
311099	Coding	4	804	atcatctgggtgcacctgat	76	47	2
311100	Coding	4	810	atccacatcatctgggtgca	80	48	2
311101	Coding	4	815	agttatccacatcatctgg	43	49	2
311102	Coding	4	892	ccttttactgttccagtc	81	50	2
311103	Coding	4	900	ctgaccttcttttactg	68	51	2
311104	Coding	4	906	agactgctgaccttctttt	63	52	2
311105	Coding	4	1029	tccattctgcatctgttcc	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	ctgtggctggtagccaacag	52	66	2
311119	Coding	4	1343	acaatattcttctaagag	27	67	2

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ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
311120	Coding	4	1405	atttcactacctgttgaag	67	68	2
311121	Coding	4	1418	acttggcctttaattcac	55	69	2
311122	Coding	4	1423	acagcacttggcctttaat	63	70	2
311123	Coding	4	1434	gaacatgacagacagcactt	62	71	2
311124	Coding	4	1551	gttcttcacattggtgttg	68	72	2
311125	Coding	4	1556	ctagagtcttcacattggt	56	73	2
311126	Coding	4	1706	ccatctcttctgttaccat	77	74	2
311127	Coding	4	1862	ttactctgatccgcattgat	49	75	2
311128	Coding	4	1871	gagatgcctttactctgatc	67	76	2
311129	Coding	4	1876	tggaggagatgcctttactc	84	77	2
311130	Coding	4	1881	agtgtctggaggagatgcctt	75	78	2
311131	Coding	4	1953	gaaattctctgccggccggg	70	79	2
311132	Coding	4	1958	ttcctgaaattctctgccgg	67	80	2
311133	Coding	4	1967	agaccactattcctgaaatt	15	81	2
311134	Coding	4	1990	ggacaatggttacaggaggg	68	82	2
311135	Coding	4	1995	tggctggacaatggttacag	80	83	2
311136	Coding	4	2276	gtctcaggagcaaagttaga	48	84	2
311137	Coding	4	2339	cactgtggccagacaccac	65	85	2
311138	Coding	4	2349	ctggccctgccactgtggcc	42	86	2
311139	Coding	4	2354	ggctgctggccctgccactg	85	87	2
311140	Coding	4	2507	ggaaacatagtttagatcagg	66	88	2
311141	Stop Codon	4	2531	caatagttctattctgaaaa	21	89	2
311142	Stop Codon	4	2537	tcacccaatagtctattc	27	90	2
311143	Stop Codon	4	2542	tatctcaccccaatagttc	24	91	2
311144	3'UTR	4	2616	agaggaacttttattctgtt	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	gtccaggccccatctatcat	57	95	2
311148	3'UTR	4	4429	tgaaaatcttctgtacatgt	72	96	2
311149	5'UTR	19	231	ccaggtggtcacatctggtc	33	97	2
311150	Exon1: Exon1A junction	20	162	tgagtccaagatcaggcggg	18	98	2

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

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HIF1-beta mRNA.

Example 16**Antisense inhibition of mouse HIF1-beta expression by chimeric phosphorothioate****5 oligonucleotides having 2'-MOE wings and a deoxy gap.**

In accordance with the present invention, a second series of antisense compounds was designed to target different 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 SITE	SEQUENCE (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	99	51989	tcatactgcctgcagcctg	59	107	2

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ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
	11 junction						
347989	5'UTR	11	3	agattaggcaccttaccgcc	80	108	2
347990	Start Codon	11	98	gccgccatggctcgagatggc	73	109	2
347991	Start Codon	11	111	gttagctgtagtcgcccca	88	110	2
347992	Coding	11	121	tcattctgggttagctgta	75	111	2
347993	Coding	11	131	acatctgatgtcatttctgg	79	112	2
347994	Coding	11	163	ttccagaagcaatggtggga	69	113	2
347995	Coding	11	195	agctcctccacctgaatcc	41	114	2
347996	Coding	11	221	cgctcgcttaatagccctctg	81	115	2
347997	Coding	11	231	cagccctgaccgtcgcttaa	83	116	2
347998	Coding	11	241	catcaaatccagccctgac	29	117	2
347999	Coding	11	317	ctggcaaacggctctttgtc	47	118	2
348000	Coding	11	327	atcatccgacctggcaaac	85	119	2
348001	Coding	11	337	agctctgctcatcatccgac	41	120	2
348002	Coding	11	355	gtctctctttatccgcagag	89	121	2
348003	Coding	11	362	ctggcaagtctctttatc	66	122	2
348004	Coding	11	367	ttccctggcaagtctctct	56	123	2
348005	Coding	11	372	atgattttccctggcaagtc	75	124	2
348006	Coding	11	414	gtaagctgtcatcttgtcc	73	125	2
348007	Coding	11	424	gttctgtgatgtaagctgtc	49	126	2
348008	Coding	11	477	tagcttgtctggtttcgag	63	127	2
348009	Coding	11	591	caaatgttcagttcctgat	82	128	2
348010	Coding	11	622	taaacagaaagccatctgct	83	129	2
348011	Coding	11	686	tgggtcaaacgggagtcac	39	130	2
348012	Coding	11	763	gctgctctcgaagttatcc	58	131	2
348013	Coding	11	858	gcacatctcatggaagact	90	132	2
348014	Coding	11	929	ttcatggaacagggtccac	84	133	2
348015	Coding	11	939	gtcagctatcatggaagaa	76	134	2
348016	Coding	11	949	tcctcaaaaagctcagtcta	56	135	2
348017	Coding	11	959	ctgcatctgttctcaaaaa	86	136	2
348018	Coding	11	1015	tgagtgaggactaccacaaag	68	137	2
348019	Coding	11	1081	ggccagcctctgggtcatca	89	138	2
348020	Coding	11	1097	cagaatttgctcccctggcc	73	139	2
348021	Coding	11	1107	ggccactaggcagaatttgc	79	140	2
348022	Coding	11	1119	cagcctgccaatggccacta	70	141	2
348023	Coding	11	1211	gtgaatatccctcaatgtt	74	142	2
348024	Coding	11	1241	acagtagccacacaacgatg	79	143	2
348025	Coding	11	1291	gacaaaattctacaatatc	53	144	2
348026	Coding	11	1302	gtcttcaggatgacaaaatt	79	145	2
348027	Coding	11	1312	gaagttgttggtcttcagga	65	146	2
348028	Coding	11	1323	gctgtctcttagaagtgtt	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	gtggttctctgctagagttc	58	151	2
348033	Coding	11	1550	gtcggacctagctgtgacct	80	152	2
348034	Coding	11	1579	ctgtacctatcttagggat	79	153	2
348035	Coding	11	1651	ccagcccatctcttctggt	23	154	2
348036	Coding	11	1681	ggacagaaacctgggaatga	76	155	2
348037	Coding	11	1719	gggcttgctgtgttctgatc	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

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ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE (5' to 3')	% INHIB	SEQ ID NO	CONTROL SEQ ID NO
348041	Coding	11	1875	gttagggagggaatgagctgc	69	160	2
348042	Coding	11	1906	cactattcctgaaattctct	65	161	2
348043	Coding	11	1958	atctgccctgcagaagatga	58	162	2
348044	Coding	11	2083	aagaacgagctctggctgta	70	163	2
348045	Coding	11	2110	tctgaaagttgtcacacca	51	164	2
348046	Coding	11	2219	gtctcaggaggaaagtggga	88	165	2
348047	Coding	11	2287	cctgccactgtggccagaca	77	166	2
348048	Coding	11	2379	ttctgaaagacctcaggct	52	167	2
348049	Coding	11	2399	tctccagcatggacagcat	68	168	2
348050	Stop Codon	11	2475	ccaatagtctattcgaaa	87	169	2
348051	3'UTR	11	2538	tctgttacaaaagatttgc	78	170	2
348052	5'UTR	100	10	cggaaatccaagatggcggac	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	agactttccccacatatc	67	175	2
348057	5'UTR	103	50	taacctatgtattcagtgat	34	176	2
311090	Coding	11	431	tctgacagttctgtgatgta	75	38	2
311091	Coding	11	464	tttcgagccagggcactaca	82	39	2
311112	Coding	11	1157	ttactcatgtctgtacagtt	82	60	2
311129	Coding	11	2819	tggaggagatgcctttactc	75	77	2
311130	Coding	11	1824	agtgtctggaggagatgcctt	78	78	2

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 168-175 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

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

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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).

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

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).

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

5 Example 19

Expression of HIF1-beta in various human cell lines

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
 10 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, OR). Hypoxic treatments of cells ($0.5-0.8 \times 10^6$ /60 mm dish or $1-2 \times 10^6$ /100 mm dish) were performed at 1% O₂ in a chamber controlled by ProOx oxygen sensor (BioSpherix, Redfield,
 15 NY) 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 μ M) was added to the cells to mimic hypoxic condition in some experiments.

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),
 20 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
 25 (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

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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).

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 CoCl_2 (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 CoCl_2 .

Example 20

Antisense modulation of HIF1-beta mRNA expression in cancer cells (dose response)

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 $\mu\text{g}/\text{ml}$ 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.

The transfection medium (120 $\mu\text{l}/\text{well}$) 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.

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 RibogreenTM (Molecular Probes).

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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

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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

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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.

15 Example 21

Antisense modulation of HIF1-beta protein expression

U87-MG cells were plated in 10 cm dishes ($1-2 \times 10^6$ 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
20 (3 μ g/ ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen).

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.

Following incubation at normoxia or hypoxia, transfected cells were harvested and
25 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-

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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).

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 oligonucleotide, 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

Genes whose products are significantly induced by hypoxia (or CoCl_2 , 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% O_2), hypoxia (1% O_2) and in the presence of 150 μM CoCl_2 , 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 RibogreenTM (Molecular Probes).

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Table 8
VEGF, GLUT-1, PGK-1, PAI-1 and Epo mRNA expression levels at normoxia, hypoxia and 150 μ M CoCl₂ (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

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 μ M CoCl₂. As previously reported, hypoxia-induced Epo expression occurred only in Hep3B cells.

Example 23

Antisense inhibition of HIF1-beta target genes

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 μ g/ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen).

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The transfection medium (120 μ l/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.

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 μ l reaction volumes. The level of mRNA for each gene was normalized to the amount of total RNA determined by RibogreenTM (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

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

U87-MG, HeLa or Hep3B cells were plated in 10 cm dishes ($1-2 \times 10^6$ 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 μ g/ml per 100 nM oligonucleotide) in Opti-Mem media (Invitrogen).

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.

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.

Under hypoxic conditions, VEGF protein production in U87-MG cells treated with HIF1-beta antisense oligonucleotide was significantly reduced (approximately 4-fold) relative to

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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*

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 1h. Samples were extracted with phenol-chloroform-isoamylalcohol, ethanol-precipitated overnight at -80°C and the DNA was resuspended in water.

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)

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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.

5 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

10 Inhibition of HIF1-beta expression in vivo

C57Bl/6 mice are maintained on a standard rodent diet and are used as control animals. Seven-week old male C57Bl/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
15 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

20 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.,
25 (2002) Cancer Research 62:2034-42), which supports the use of *in vitro* tube formation as an endpoint for angiogenesis.

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
30 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,

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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.

The tube formation assay is performed using an *in vitro* Angiogenesis Assay Kit (Chemicon International, Temecula, CA), or growth factor reduced Matrigel (BD Biosciences, Bedford, MA). 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 75nM oligonucleotide in lipofectin (Gibco, Grand Island, NY). Approximately 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.

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

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**

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**

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, OR). 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.

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.

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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, CA). 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.

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.

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What is claimed is:

1. An antisense oligonucleotide 13 to 50 nucleobases in length which is specifically hybridizable with a nucleic acid molecule encoding human HIF1-beta, said
5 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.
- 10 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
15 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.
- 20 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.
- 25 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.

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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 an animal an antisense oligonucleotide of claim 1 such that aberrant angiogenesis is prevented or inhibited.

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<223> n = A,T,C or G

<220>

<221> misc_feature

<222> 217, 441, 498

<223> n = A,T,C or G

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<213> H. sapiens

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt 20

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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ctgtggctgg tagccaacag

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ISIS-5768.ST25.txt

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<223> Antisense Compound

<400> 70

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<210> 71

<211> 20

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<223> Antisense Compound

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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ISIS-5768.ST25.txt

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