MODULATION OF ENDOTHELIAL LIPASE EXPRESSION

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Appl. No.: 11/502,251
Filed: Aug. 9, 2006

Related U.S. Application Data

Continuation-in-part of application No. 10/319,915, filed on Dec. 12, 2002,
Continuation-in-part of application No. 11/036,095, filed on Jan. 14, 2005, which is a continuation-in-part of application No. 10/187,110, filed on Jun. 29, 2002, now abandoned, and which is a continuation-in-part of application No. 10/303,328, filed on Nov. 22, 2002, now abandoned, and which is a continuation-in-part of application No. 10/302,028, filed on Nov. 21, 2002, now abandoned, and which is a continuation-in-part of application No. 10/293,866, filed on Nov. 11, 2002, now abandoned, and which is a continuation-in-part of application No. 10/316,241, filed on Dec. 9, 2002, now abandoned, and which is a continuation-in-part of application No. 10/317,401, filed on Dec. 11, 2002, now abandoned, and which is a continuation-in-part of application No. 10/210,556, filed on Jul. 31, 2002, now abandoned, and which is a continuation-in-part of application No. 10/210,723, filed on Jul. 31, 2002, now abandoned, and which is a continuation-in-part of application No. 10/308,589, filed on Dec. 11, 2002, now abandoned, and which is a continuation-in-part of application No. 10/302,027, filed on Nov. 21, 2002, now abandoned, and which is a continuation-in-part of application No. 10/300,399, filed on Nov. 19, 2002, now abandoned, and which is a continuation-in-part of application No. 10/189,429, filed on Jul. 3, 2002, now abandoned, and which is a continuation-in-part of application No. 10/174,020, filed on Jun. 17, 2002, now abandoned, and which is a continuation-in-part of application No. 10/177,554, filed on Jun. 20, 2002, now abandoned, and which is a continuation-in-part of application No. 10/185,035, filed on Jun. 28, 2002, now abandoned, and which is a continuation-in-part of application No. 10/316,755, filed on Dec. 10, 2002, now abandoned, and which is a continuation-in-part of application No. 10/316,389, filed on Dec. 10, 2002, now abandoned, and which is a continuation-in-part of application No. 10/292,312, filed on Nov. 11, 2002, now abandoned, and which is a continuation-in-part of application No. 10/159,266, filed on May 31, 2002, now abandoned, and which is a continuation-in-part of application No. 10/319,893, filed on Dec. 12, 2002, now abandoned, and which is a continuation-in-part of application No. 10/317,869, filed on Dec. 11, 2002, now abandoned, and which is a continuation-in-part of application No. 10/300,820, filed on Nov. 19, 2002, now abandoned, and which is a continuation-in-part of application No. 10/319,915, filed on Dec. 12, 2002.

Publication Classification

Int. Cl.
C12Q 1/68 (2006.01)
C07H 21/02 (2006.01)
C07F 9/6512 (2007.01)

U.S. Cl. ........................................ 435/6; 536/23.1; 544/243

ABSTRACT

Compounds, compositions and methods are provided for modulating the expression of endothelial lipase. The compositions comprise oligonucleotides, targeted to nucleic acid encoding endothelial lipase. Methods of using these compounds for modulation of endothelial lipase expression and for diagnosis and treatment of disease associated with expression of endothelial lipase are provided.
MODULATION OF ENDOTHELIAL LIPASE EXPRESSION

RELATED APPLICATIONS


FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

Atherosclerosis is the major causative factor of heart disease and stroke, and the leading cause of death in Western countries is cardiovascular disease. Dyslipidemia is a primary contributory factor to atherosclerosis. Because triglycerides are insoluble in the bloodstream, they are packaged for plasma transport in micelle-like lipoprotein particles composed of protein and phospholipid shells surrounding a non-polar core of acylglycerols, free cholesterol, and cholesterol esters. Lipoproteins have been classified into five broad categories on the basis of their functional and physical properties: chylomicrons (which transport dietary lipids from intestine to tissues); very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low density lipoproteins (LDL), (all of which transport triglycerides and cholesterol from the liver to tissues); and high density lipoproteins (HDL) (which transport endogenous cholesterol from tissues to the liver, as well as mediating selective cholesterol ester delivery to steroidogenic tissues). All of these particles undergo continuous metabolic processing and have somewhat variable properties and compositions. Plasma concentrations of LDL and HDL are directly and inversely related, respectively, to the risk of atherosclerotic cardiovascular disease (Krieger, Proc. Natl. Acad. Sci. U. S. A., 1998, 95, 4077-4080).

[0004] HDL protect the arterial wall from the development of atherosclerosis by promoting efflux of excess cholesterol from cells in the arterial wall and returning it to the liver for excretion into the bile, as well as by protecting LDL from oxidation, thereby reducing the inflammatory response of epithelial cells, inhibiting the coagulation pathway, and promoting the availability of nitric oxide. The metabolism of HDL is influenced by several members of the triacylglycerol (TG) lipase family of proteins, which hydrolyze triglycerides, phospholipids and cholesterol esters, generating fatty acids to facilitate intestinal absorption, energy production or storage. Of the TG lipases, lipoprotein lipase (LPL) influences the metabolism of HDL cholestero by hydrolyzing triglycerides in triglyceride-rich lipoproteins, resulting in the transfer of lipids and apolipoproteins to HDL and is responsible for hydrolyzing chylomicron and VLDL in muscle and adipose tissues. Hepatic lipase (HL) hydrolyzes HDL triglyceride and phospholipids, generating smaller, lipid-depleted HDL particles, and plays a role in the uptake of HDL cholesterol (Jin et al., Trends Endocrinol. Metab., 2002, 13, 174-178; Wong and Schotz, J. Lipid Res., 2002, 43, 993-999). Endothelial lipase (also known as EDL, EL, LIPG, endothelial-derived lipase and endothelial cell-derived lipase) was identified using differential display to isolate mRNAs which were differentially regulated in response to oxidized-LDL (Jaye et al., Nat. Genet., 1999, 21, 424-428).

[0005] Independently, the human endothelial lipase gene was identified in human umbilical vein endothelial cells (HUVECs) undergoing tube formation in a model of vascular formation (Hirata et al, J Biol. Chem., 1999, 274, 14170-14175).

[0006] In humans, the endothelial lipase gene has been assigned to chromosome 18, and the rat endothelial lipase gene was identified and mapped to rat chromosome 18 in the vicinity of a quantitative trait locus that affects serum HDL levels after a high fat diet (Bonnet et al., DNA Seq., 2001, 12, 285-287).

[0007] At least 50% of the variation in HDL cholesterol levels is genetically determined. The phenotype of elevated HDL cholesterol is often dominantly inherited, but homozygous deficiency of HL or of the cholesteryl ester transfer protein (CETP), which result in elevated HDL cholesterol, are recessive conditions. Recently, several genetic variations in the human endothelial lipase gene have been identified, of which potentially produce functional variants of the protein, and the frequencies of these variants were found to be associated with elevated levels of HDL cholesterol in human subjects (del.emos et al., Circulation, 2002, 106, 1321-1326).

[0008] Notably, the endothelial lipase-mediated binding and uptake of HDL particles and the selective uptake of HDL-derived cholesterol esters have been reported to be independent of its enzymatic lipolytic activity (Strauss et al., Biochem. J., 2002).

[0009] Recombinant endothelial lipase protein has substantial phospholipase activity but has been reported to have less hydrolytic activity toward triglyceride lipids (Hirata et al, J. Biol. Chem., 1999, 274, 14170-14175; Jaye et al., Nat. Genet., 1999, 21, 424428). However, endothelial lipase does exhibit triglyceride lipase activity ex vivo in addition to its HDL phospholipase activity, and endothelial lipase was found to hydrolyze HDL more efficiently than other lipo-

[0010] On the basis of its amino acid sequence homology to other members of the TG lipase family, including the
presence of a characteristic 19-amino acid “lid” domain predicted to form an amphipathic helix covering the cata-
lytic pocket of the enzyme and confers substrate specificity to the enzymes of the TG lipase family, and its demonstrated
phospholipase activity, the endothelial lipase protein is believed to be involved in lipoprotein metabolism and

[0011] Endothelial lipase was cloned from epithelial cells
but has been demonstrated to be abundantly expressed in
a variety of tissues including ovary, testis, thyroid gland, liver,
lung, kidney and placenta, the latter suggesting the potential
for a role in development (Hirata et al., J. Biol. Chem., 1999,
274, 14170-14175; Jaye et al., Nat. Genet., 1999, 21,
424428). Interestingly, endothelial lipase mRNA levels were
upregulated in HUVEC and coronary artery endothelial cells
upon treatment with inflammatory cytokines implicated in
vascular disease etiology and vascular remodeling, including
TNF-alpha and IL-1 beta. Thus, endothelial lipase is
predicted to be intricately involved in modulating vessel
wall lipid metabolism and to play a role in vascular diseases
such as atherosclerosis (Hirata et al., Biochem. Biophys. Res.

[0012] Disclosed and claimed in U.S. Patent 6,395,530 is
an isolated nucleic acid which hybridizes at high stringency
to a nucleic acid having a sequence selected from a group of
which endothelial lipase is a member or to a target consisting
of nucleotides from 44-79 of the endothelial lipase gene
wherein the complement of said isolated nucleic acid encodes
a polypeptide having trisacylglycerol lipase or phospho-
lipase A activity. Further claims are a vector, a compo-

istion, a recombinant cell and method for preparing a
polypeptide. Antisense nucleic acids are generally disclosed
(Jaye et al., 2002).

[0013] Disclosed and claimed in PCT Publications WO
01/40466 and WO 00/73452 is an isolated nucleic acid
having at least 80% nucleic acid sequence identity to a
nucleotide sequence that encodes the endothelial lipase protein
or to a nucleotide sequence selected from a group of
which the endothelial lipase gene is a member, a vector, a
host cell, a process for producing a polypeptide, an isolated
polypeptide, a chimeric molecule, and antibody, a method of
detecting said polypeptide in a sample, a method of linking
a bioactive molecule to a cell expressing said polypeptide,
a method of modulating at least one biological activity of a
cell expressing said polypeptide, methods for stimulating the
release of TNF-alpha from human blood, for modulating the
uptake of glucose or FFA by skeletal muscle or adipocyte
cells, for stimulating the proliferation or differentiation of
chondrocyte cells, for stimulating the proliferation of inner
ear utricular supporting cells, endothelial cells or T-lympho-
cyte cells, for stimulating the proliferation of or gene expres-
sion in pericyte cells, for stimulating the release of pro-
teoglycans from cartilage, for stimulating the release of a
cytokine from PBMC cells, for inhibiting the binding of
A-peptide to factor VIIA, for inhibiting the differentiation of
adipocyte cells, for detecting the presence of tumor in an
mammal, an oligonucleotide probe derived from any of
several nucleotide sequences cited, a composition useful for
the treatment of immune related diseases, use of a polypep-
tide to prepare said composition, a method of diagnosing an
immune related disease in a mammal, an immune related
disease diagnostic kit, a method for identifying an agonist or
a compound capable of inhibiting the expression and/or
activity of a polypeptide, a vector, and an ex vivo producer
cell. Antisense oligonucleotide agonists or antagonists are
generally disclosed (Ashkenazi et al., 2000; Baker et al.,
2001).

01/96388 is an isolated polynucleotide comprising a
sequence selected from a group of nucleotide sequences,
complements of said sequences, sequences consisting of
at least 20 contiguous residues of one of said sequences,
sequences that hybridize to said sequences, sequences hav-
ing at least 75% identity to said sequence, and degenerate
variants of said sequence, an isolated polypeptide, an
expression vector, a host cell, an isolated antibody, a method
for detecting the presence of a cancer in a patient, a fusion
protein, an oligonucleotide that hybridizes to said sequence,
a method for stimulating and/or expanding T cells specific
for a tumor protein, an isolated T cell population, a com-
position comprising a first component selected from the
group consisting of physiologically acceptable carriers and
immunostimulants, and a second component selected from
the group consisting of said polypeptides, polynucleotides,
antibodies, fusion proteins, T cell populations and antigen
presenting cells that express a polypeptide, a method for
stimulating an immune response in a patient, a method for
the treatment of a cancer in a patient, a method for deter-

mining the presence of a cancer in a patient, a diagnostic
kit comprising at least one oligonucleotide or antibody, and
a method for inhibiting the development of a cancer in a
patient. Antisense oligonucleotides are generally disclosed
(Jiang et al., 2001).

[0015] Currently, there are no known therapeutic agents
which effectively inhibit the synthesis of endothelial lipase.

[0016] Consequently, there remains a long felt need for
agents capable of effectively inhibiting endothelial lipase
function.

[0017] Antisense technology is emerging as 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 endothelial lipase expression.

[0018] The present invention provides compositions and
methods for modulating endothelial lipase expression.

SUMMARY OF THE INVENTION

[0019] The present invention is directed to compounds,
especially nucleic acid and nucleic acid-like oligomers,
which are targeted to a nucleic acid encoding endothelial
lipase, and which modulate the expression of endothelial
lipase. Pharmaceutical and other compositions comprising
the compounds of the invention are also provided. Further
provided are methods of screening for modulators of endot-

ehal lipase and methods of modulating the expression of
endothelial lipase in cells, tissues or animals comprising contacting said cells, tissues or animals with one or more of the compounds or compositions of the invention. Methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of endothelial lipase are also set forth herein. Such methods comprise administering a therapeutically or prophylactically effective amount of one or more of the compounds or compositions of the invention to the person in need of treatment.

**DETAILED DESCRIPTION OF THE INVENTION**

**A. Overview of the Invention**

[0020] The present invention employs compounds, preferably oligonucleotides and similar species for use in modulating the function or effect of nucleic acid molecules encoding endothelial lipase. This is accomplished by providing oligonucleotides which specifically hybridize with one or more nucleic acid molecules encoding endothelial lipase. As used herein, the terms “target nucleic acid” and “nucleic acid molecule encoding endothelial lipase” have been used for convenience to encompass DNA encoding endothelial lipase, RNA (including pre-mRNA and MRNA or portions thereof) transcribed from such DNA, and also cDNA derived from such RNA. The hybridization of a compound of this invention with its target nucleic acid is generally referred to as “antisense”. Consequently, the preferred mechanism believed to be included in the practice of some preferred embodiments of the invention is referred to herein as “antisense inhibition.” Such antisense inhibition is typically based upon hydrogen bonding-based hybridization of oligonucleotide strands or segments such that at least one strand or segment is cleaved, degraded, or otherwise rendered inoperable. In this regard, it is presently preferred to target specific nucleic acid molecules and their functions for such antisense inhibition.

[0021] The functions of DNA to be interfered with can include replication and transcription. Replication and transcription, for example, can be from an endogenous cellular template, a vector, a plasmid construct or otherwise. The functions of RNA to be interfered with can include functions such as translocation of the RNA to a site of protein synthesis, translation of the RNA to sites within the cell which are distant from the site of RNA synthesis, translation of protein from the RNA, splicing of the RNA to yield one or more RNA species, and catalytic activity or complex formation involving the RNA which may be engaged in or facilitated by the RNA. One preferred result of such interference with target nucleic acid function is modulation of the expression of endothelial lipase. 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.

[0022] Inhibition is often the preferred form of modulation of expression and mRNA is often a preferred target nucleic acid.

[0023] 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.

[0024] An antisense compound is specifically hybridizable when binding of the compound to the target nucleic acid interferes with the normal function of the target nucleic acid to cause a loss of activity, and 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.

[0025] 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 further 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.

[0026] It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. Moreover, an oligonucleotide may hybridize over one or more segments such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure or hairpin structure). It is preferred that the antisense compounds of the present invention comprise at least 70% sequence complementarity to a target region within the target nucleic acid, more preferably that they comprise 90% sequence complementarity and even more preferably comprise 95% sequence complementarity to the target region within the target nucleic acid sequence to which they are targeted. For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In
this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having 4 (four) noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul et al., J. Mol. Biol., 1990, 215, 403-410; Zhang and Madden, Genome Res., 1997, 7, 649-656).

B. Compounds of the Invention

[0027] According to the present invention, compounds include antisense oligomeric compounds, antisense oligonucleotides, ribozymes, external guide sequence (EGS) oligonucleotides, alternate splicers, primers, probes, 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.

[0028] While the preferred 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.

[0029] The first evidence that dsRNA could lead to gene silencing in animals came in 1995 from work in the nematode, Caenorhabditis elegans (Guo and Kempheus, Cell, 1995, 81, 611-620). Montgomery et al. have shown that the primary interference effects of dsRNA are posttranscriptional (Montgomery et al., Proc. Natl. Acad. Sci. U.S.A. 1998, 95, 15502-15507). The posttranscriptional antisense mechanism defined in Caenorhabditis elegans resulting from exposure to double-stranded RNA (dsRNA) has since been designated RNA interference (RNAi). This term has been generalized to mean antisense-mediated gene silencing involving the introduction of dsRNA leading to the sequence-specific reduction of endogenous targeted mRNA levels (Fire et al., Nature, 1998, 391, 806-811). Recently, it has been shown that it is, in fact, the single-stranded RNA oligomers of antisense polarity of the dsRNAs which are the potent inducers of RNAi (Tijsterman et al., Science, 2002, 295, 694-697).

[0030] In the context of this invention, the term "oligomeric compound" refers to a polymer or oligomer comprising a plurality of monomeric units. In the context of this invention, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or mimetics, chimeras, analogs and homologs thereof. This term includes oligonucleotides composed of naturally occurring nucleobases, sugars and covalent internucleoside (backbone) linkages as well as oligonucleotides having non-naturally occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for a target nucleic acid and increased stability in the presence of nucleases.

[0031] While oligonucleotides are a preferred form of the compounds of this invention, the present invention comprehends other families of compounds as well, including but not limited to oligonucleotide analogs and mimetics such as those described herein.

[0032] The compounds in accordance with this invention preferably comprise from about 8 to about 80 nucleobases (i.e. from about 8 to about 80 linked nucleosides). One of ordinary skill in the art will appreciate that the invention embodies 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 in length.

[0033] In one preferred embodiment, the compounds of the invention are 12 to 50 nucleobases in length. One having ordinary skill in the art will appreciate that this embodies compounds of 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, or 50 nucleobases in length.

[0034] In another preferred embodiment, the compounds of the invention are 15 to 30 nucleobases in length. One having ordinary skill in the art will appreciate that this embodies compounds of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length.

[0035] Particularly preferred compounds are oligonucleotides from about 12 to about 50 nucleobases, even more preferably those comprising from about 15 to about 30 nucleobases.

[0036] Antisense compounds 8-80 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.

[0037] Exemplary preferred antisense compounds include oligonucleotide sequences that comprise at least the 8 consecutive nucleobases from the 5'-terminus of one of the illustrative preferred antisense compounds (the remaining nucleobases being a consecutive stretch of the same oligonucleotide beginning immediately upstream of the 5'-termi-
nus of the antisense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 8 to about 80 nucleobases). Similarly preferred antisense compounds are represented by oligonucleotide sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative preferred 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 8 to about 80 nucleobases). One having skill in the art armed with the preferred antisense compounds illustrated herein will be able, without undue experimentation, to identify further preferred antisense compounds.

[0038] 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 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 endothelial lipase.

[0039] The targeting process usually also includes determination of at least one target region, segment, or site within the target nucleic acid for the antisense interaction to occur such that the desired effect, e.g., modulation of expression, will result. Within the context of the present invention, the term “region” is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic. Within regions of target nucleic acids are segments. “Segments” are defined as smaller or sub-portions of regions within a target nucleic acid. “Sites,” as used in the present invention, are defined as positions within a target nucleic acid.

[0040] Since, as is known in the art, the translation initiation codon is typically 5'-AUG (in transcribed mRNA molecules; 5'-ATG in the corresponding DNA molecule), the translation initiation codon is also referred to as the “AUG codon,” the “start codon” or the “AUG start codon”. A minority of genes have a translation initiation codon having the RNA sequence 5'-GUG, 5'-UUG or 5'-CUG, and 5'-AUA, 5'-ACG and 5'-CUA have been shown to function in vivo. Thus, the terms “translation initiation codon” and “start codon” can encompass many codon sequences, even though the initiator amino acid in each instance is typically methionine (in eukaryotes) or formylmethionine (in prokaryotes). It is also known in the art that eukaryotic and prokaryotic genes may have two or more alternative start codons, any one of which may be preferentially utilized for translation initiation in a particular cell type or tissue, or under a particular set of conditions. 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 encoding endothelial lipase, regardless of the sequence(s) of such codons. It is also known in the art that a translation termination codon (or “stop codon”) of a gene may have one of three sequences, i.e., 5'-UAA, 5'-UAG and 5'-UGA (the corresponding DNA sequences are 5'-TAA, 5'-TAG and 5'-TGA, respectively).

[0041] The terms “start codon region” and “translation initiation 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 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.

[0042] Consequently, the “start codon region” (or “translation initiation codon region”) and the “stop codon region” (or “translation termination codon region”) are all regions which may be targeted effectively with antisense compounds of the present invention.

[0043] The open reading frame (ORF) or “coding region,” which is known in the art to refer to the region between the translation initiation codon and the translation termination codon, is also a region which may be targeted effectively. Within the context of the present invention, a preferred region is the intragenic region encompassing the translation initiation or termination codon of the open reading frame (ORF) of a gene.

[0044] Other target regions include the 5' untranslated region (5'UTR), known in the art to refer 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' untranslated region (3'UTR), known in the art to refer to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA (or corresponding nucleotides on the gene). The 5' cap site of an mRNA comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage. The 5' cap region of an mRNA is considered to include the 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap site. It is also preferred to target the 5' cap region.

[0045] 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. 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 overproduction of a particular splice product is implicated in disease. Aberrant fusion junctions due to rearrangements or deletions are also preferred target sites. mRNA transcripts produced via the process of splicing of two (or more) mRNAs from different gene sources are known as “fusion transcripts”. It is also known that introns can be effectively targeted using antisense compounds targeted to, for example, DNA or pre-mRNA.

[0046] 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.

[0047] 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.

[0048] 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 that 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 poly(A) variant in which the multiple transcripts produced result from the alternative selection of one of the poly(A) stop signals by the transcription machinery, thereby producing transcripts that terminate at unique poly(A) sites. Within the context of the invention, the types of variants described herein are also preferred target nucleic acids.

[0049] The locations on the target nucleic acid to which the preferred antisense compounds hybridize are hereinbelow referred to as “preferred target segments.” As used herein the term “preferred target segment” is defined as at least an 8-nucleobase portion of a target region to which an active antisense compound is targeted. While not wishing to be bound by theory, it is presently believed that these target segments represent portions of the target nucleic acid which are accessible for hybridization.

[0050] While the specific sequences of certain preferred target segments are set forth herein, one of skill in the art will recognize that these serve to illustrate and describe particular embodiments within the scope of the present invention. Additional preferred target segments may be identified by one having ordinary skill.

[0051] Target segments 8-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative preferred target segments are considered to be suitable for targeting as well.

[0052] 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 downstream of the 3'-terminus of the target segment and continuing until the DNA or RNA contains about 8 to about 80 nucleobases). Similarly preferred target segments are represented by DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative preferred target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 5'-terminus of the target segment and continuing until the DNA or RNA contains about 8 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.

[0053] 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.

D. Screening and Target Validation

[0054] In a further embodiment, the “preferred target segments” identified herein may be employed in a screen for additional compounds that modulate the expression of endothelial lipase. “Modulators” are those compounds that decrease or increase the expression of a nucleic acid molecule encoding endothelial lipase and which comprise at least an 8-nucleobase portion which is complementary to a preferred target segment. The screening method comprises the steps of contacting a preferred target segment of a nucleic acid molecule encoding endothelial lipase with one or more candidate modulators, and selecting for one or more candidate modulators which decrease or increase the expression of a nucleic acid molecule encoding endothelial lipase. Once it is shown that the candidate modulator or modulators are capable of modulating (e.g. either decreasing or increasing) the expression of a nucleic acid molecule encoding endothelial lipase, the modulator may then be employed in further investigative studies of the function of endothelial lipase, or for use as a research, diagnostic, or therapeutic agent in accordance with the present invention.

[0055] The preferred target segments of the present invention may be also be combined with their respective complementary antisense compounds of the present invention to form stabilized double-stranded (duplexed) oligonucleotides.


[0057] The compounds of the present invention can also be applied in the areas of drug discovery and target validation. The present invention comprehends the use of the compounds and preferred target segments identified herein in drug discovery efforts to elucidate relationships that exist between endothelial lipase and a disease state, phenotype, or
condition. These methods include detecting or modulating endothelial lipase comprising contacting a sample, tissue, cell, or organism with the compounds of the present invention, measuring the nucleic acid or protein level of endothelial lipase and/or a related phenotypic or chemical endpoint at some time after treatment, and optionally comparing the measured value to a non-treated sample or sample treated with a further compound of the invention. These methods can also be performed in parallel or in combination with other experiments to determine the function of unknown genes for the process of target validation or to determine the validity of a particular gene product as a target for treatment or prevention of a particular disease, condition, or phenotype.

E. Kits, Research Reagents, Diagnostics, and Therapeutics

[0058] The compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. Furthermore, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes or to distinguish between functions of various members of a biological pathway.

[0059] 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.

[0060] 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.


[0062] The compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding endothelial lipase. For example, oligonucleotides that are shown to hybridize with such efficiency and under such conditions as disclosed herein as to be effective endothelial lipase inhibitors will also be effective primers or probes under conditions favoring gene amplification or detection, respectively. These primers and probes are useful in methods requiring the specific detection of nucleic acid molecules encoding endothelial lipase and in the amplification of said nucleic acid molecules for detection or for use in further studies of endothelial lipase. Hybridization of the antisense oligonucleotides, particularly the primers and probes, of the invention with a nucleic acid encoding endothelial lipase can be detected by means known in the art. Such means may include conjugation of an enzyme to the oligonucleotide, radiolabelling of the oligonucleotide or any other suitable detection means. Kits using such detection means for detecting the level of endothelial lipase in a sample may also be prepared.

[0063] The specificity and sensitivity of antisense is also harnessed by those of skill in the art for therapeutic uses. Antisense compounds have been employed as therapeutic moieties in the treatment of disease states in animals, including humans. Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that antisense compounds can be useful therapeutic modalities that can be configured to be useful in treatment regimes for the treatment of cells, tissues and animals, especially humans.

[0064] For therapeutics, an animal, preferably a human, suspected of having a disease or disorder which can be treated by modulating the expression of endothelial lipase is treated by administering antisense compounds in accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to the animal in need of treatment, a therapeutically effective amount of a endothelial lipase inhibitor. The endothelial lipase inhibitors of the present invention effectively inhibit the activity of the endothelial lipase protein or inhibit the expression of the endothelial lipase protein. In one embodiment, the activity or expression of endothelial lipase in an animal is inhibited by about 10%. Preferably, the activity or expression of endothelial lipase in an animal is inhibited by about 30%. More preferably, the activity or expression of endothelial lipase in an animal is inhibited by 50% or more.

[0065] For example, the reduction of the expression of endothelial lipase may be measured in serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal. Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding endothelial lipase protein and/or the endothelial lipase protein itself.

[0066] The 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,
F. Modifications

[0067] As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic 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 DNA and RNA is a 3' to 5' phosphodiester linkage.

Modified Internucleoside Linkages (Backbones)

[0068] Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of 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.

[0069] Preferred modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, phosphorodithioates, phosphorothionates, phosphoramidates, aminoalkylphosphonothioates, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkyl phosphonates and chiral phosphonates, phosphinites, phosphorimidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thiono-phosphonimidates, thionoalkylphosphonates, thionoalkylphosphorothionates, selenophosphates and boronophosphates having normal 3'–5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleosides 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.

[0070] Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 5,687,808; 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; 5,543,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, certain of which are commonly owned with this application, and each of which is herein incorporated by reference.

[0071] Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heterotom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heterotom or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfone and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboucetyl backbones; alkene containing backbones; sulfamate backbones; methyleneiminio and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₃ component parts.

[0072] Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, certain of which are commonly owned with this application, and each of which is herein incorporated by reference.

Modified Sugar and Internucleoside linkages—Mimetics

[0073] In other preferred oligonucleotide mimetics, both the sugar and the internucleoside linkage (i.e. the backbone), of the nucleotide units are replaced with novel groups. The nucleobase units are maintained for hybridization with an appropriate target nucleic acid. One such compound, an oligonucleotide mimic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminomethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., Science, 1991, 254, 1497-1500.

[0074] Preferred embodiments of the invention are oligonucleotides with phosphorothioate backbones and oligonucleosides with heterotom backbones, and in particular \(-\text{CH}_2-\text{NH}-\text{O-CH}_2-\), \(-\text{CH}_2-\text{N(CH}_3)_2-\text{O-CH}_2-\) [known as a methylene (methylimino) or MIM backbone], \(-\text{CH}_2-\text{O-N(CH}_3)_2-\text{CH}_2-\), \(-\text{CH}_2-\text{N(CH}_3)_2-\text{N(CH}_3)_2-\text{CH}_2-\) and \(-\text{O-N(CH}_3)_2-\text{CH}_2-\) [wherein the native phosphodiester backbone is represented as \(-\text{O-P-CH}_2-\) of the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are oligonucleotides having morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.
Modified Sugars

Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O—, S—, or N-alkyl; O—, S—, or N-alkenyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C1 to C10 alkyl or C1 to C10 alkenyl and alkynyl. Particularly preferred are O(CH2)nO(CH2)nCH2, O(CH2)nOCH2, O(CH2)nNH2, O(CH2)nCH2, O(CH2)nONH2, and O(CH2)nON [CH2]nCH2], where n and m are from 1 to about 10. Other preferred oligonucleotides comprise one of the following at the 2' position: C1 to C10 lower alkyl, substituted lower alkyl, alkyl, alkenyl, alkynyl, O—alkyl or O—alkenyl, SH, SCH2, OCN, Cl, Br, CN, CF3, OCF2, SO2CH3, SO2CH2, ONO2, NO2, NH2, heterocycloalkyl, heterocycloalkenyl, aminolaktonyl, polyalkylamino, substituted sil, a RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O—CH2CH2OCH2), also known as 2-O(2-methoxyethoxy) or 2'-MOE (Martin et al., Helv Chim Acta, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminoethoxyethoxy, i.e., a (CH2)nON(CH2)n group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminooxyethoxy (also known in the art as 2'-O-dimethyl-amino-ethoxy-ethyl or 2'-DMAE), i.e., 2'-O—CH2—O—CH2—N(CH2)2, also described in examples hereinbelow.

Modified Nucleobases

Oligonucleotides may also include nucleobase modifications or substitutions. As used herein, “unmodified” or “natural” nucleobases include the pyrimidine bases adenine (A) and guanine (G), and the purine 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-amino adenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiouracil and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (—C≡C—CH2) uracil and cytosine and other alkyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxy and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F adenine, 2-amino adenine, 8-azoguanine and 8-azaadenine, 7-deaza guanine and 7-deaza adenine and 3-deaza guanine and 3-deaza adenine. Further modified nucleobases may include tricyclic pyrimidines such as phenoxazine cytidine (H-phenazin-2(3H)-one), phenothiazine cytidine (H-phenothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-phenazin-2(3H)-one), carbazole cytidine (2H-phenazin-2(3H)-one), pyridoindole cytidine (H-pyrido[3,2,4:5]pyrrolo[2,3-d]pyrimidin-2-one), and other modified nucleobases which may also include those in which the pyrimidine base is replaced with other heterocycles, for example 7-deaza adenine, 7-deazaguanine, 2-aminopyridine, and pyridone. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J.I., ed. John Wiley & Sons, 1990, those disclosed by English et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y.S., Chapter 15, Antisense Research and Applications, pages 289-302, Crooke, S.T. and 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-azapurinimides and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynuracil 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-methoxylated sugar modifications.
patent 5,750,692, which is commonly owned with the instant application and also herein incorporated by reference.

Conjugates

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. These moieties or conjugates can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterol, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake, distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application PCT/US92/09196, filed Oct. 23, 1992, and U.S. Pat. No. 6,287,860, the entire disclosure of which are incorporated herein by reference. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioglycerol, e.g., hexyl-S-tritylthiol, a thiocholarer, an aliphatic chain, e.g., docosanediol or undecyl residues, a phospholipid, e.g., dihexadecyl-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 palmitoyl moiety, or an octadecylamine or hexylamino-carbonyl-oxycarboxylic acid moiety. Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+) naprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fluconic acid, folinic acid, benzothiadiazole, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfal drug, an anti diabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their conjugation procedures are described in U.S. Patent Application 09/334,130 (filed Jun. 15, 1999) which is incorporated herein by reference in its entirety.

Chimeric Compounds

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.

Chimeric 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.

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 endonucleases, such as RNaseE, 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.

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

Formulations

The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, such as, for example, liposomes, receptor-targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative U.S. patents that teach the preparation of such uptake, distribution and/or absorption-assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,109,921; 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;
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.

[0091] 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.

[0092] 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.

[0093] Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 µm in diameter. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Microemulsions are included as an embodiment of the present invention. Emulsions and their uses are well known in the art and are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0094] Formulations of the present invention include liposomal formulations. As used in the present invention, the term “liposome” means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or blayers. Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior that contains the composition to be delivered. Cationic liposomes are positively charged liposomes which are believed to interact with negatively charged DNA molecules to form a stable complex. Liposomes that are pH-sensitive or negatively-charged are believed to entrap DNA rather than complex with it. Both cationic and noncationic liposomes have been used to deliver DNA to cells.

[0095] Liposomes also include “sterically stabilized” liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome comprises one or more glycolipids or is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. Liposomes and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0096] The pharmaceutical compositions and formulations of the present invention may also include surfactants. The use of surfactants in drug products, formulations and emulsions is well known in the art. Surfactants and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.
In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly oligonucleotides. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Penetration enhancers and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

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

Preferred formulations for topical administration include those in which the oligonucleotides of the invention are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Preferred lipids and liposomes include neutral (e.g. dioleoylphosphatidyl DOPE ethanalamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline negative (e.g. dimyristoylphosphatidyl glycerol DMPG) and cationic (e.g. dioleoyltrimethylammonopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA).

For topical or other administration, oligonucleotides of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, oligonucleotides may be complexed to lipids, in particular to cationic lipids. Preferred fatty acids and esters, pharmaceutically acceptable salts thereof, and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety. Topical formulations are described in detail in U.S. patent application Ser. No. 09/315,298 filed on May 20, 1999, which is incorporated herein by reference in its entirety.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticles, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or mini-tablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. Preferred oral formulations are those in which oligonucleotides of the invention are administered in conjunction with one or more penetration enhancers surfactants and chelators. Preferred surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Preferred bile acids/salts and fatty acids and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety. Also preferred are combinations of penetration enhancers, for example, fatty acids/salts in combination with bile acids/salts. A particularly preferred combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. Oligonucleotides of the invention may be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. Oligonucleotide complexing agents and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety. Oral formulations for oligonucleotides and their preparation are described in detail in U.S. applications Ser. No. 09/108,673 (filed Jul. 1, 1998), Ser. No. 09/315,298 (filed May 20, 1999) and Ser. No. 10/071,822, filed Feb. 8, 2002, each of which is incorporated herein by reference in their entirety.

Compositions and formulations for parenteral, intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Certain embodiments of the invention provide pharmaceutical compositions containing one or more oligonucleic compounds and one or more other chemotherapeutic agents which function by a non-antisense mechanism. Examples of such chemotherapeutic agents include but are not limited to cancer chemotherapeutic drugs such as daunorubicin, daunomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, orosubcin, bleomycin, mafosfamide, ifosfamide, cytosine arabinoside, bis-chloroethyl nitrosourea, busulfan, mitomycin C, actinomycin D, mithramycin, prednisone, hydroxyprogesterone, testosterone, tamoxifen, dactarbazine, procarbazine, hexamethylmelamine, pentamethylmelamine, mitoxantrone, amascrine, chlorambucil, methylecyclohexyl nitrosourea, nitrogen mustards, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-azacytidine, hydroxyurea, deoxycoformycin, 4-hydroxyperoxyeclophosphoramide, 5-fluorouracil (5-FU), 5-fluorodeoxyuridine (5-FdUR), methotrexate (MTX), colchicine, taxol, vincristine, vinblastine, etoposide (VP-16), trimetrexate, irinotecan, topotecan, gemcitabine, teniposide, cisplatin and diethylstilbestrol (DES). When used with the compounds of the invention, such chemotherapeutic agents may be used individually (e.g., 5-FU and oligonucleotide), sequentially (e.g., 5-FU and oligonucleotide for a period of time followed by MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide).

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.

H. 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. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC50 found to be effective in vitro and in vivo animal models. In general, dosage is from 0.01 ug to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the oligonucleotide is administered in maintenance doses, ranging from 0.01 ug to 100 g per kg of body weight, once or more daily, to once every 20 years.

[0106] While the present invention has been described with specificity in accordance with certain of its preferred embodiments, the following examples serve only to illustrate

**EXAMPLES**

**Example 1**

**Synthesis of Nucleoside Phosphoramiidites**

[0107] The following compounds, including amides and their intermediates were prepared as described in U.S. Pat. No. 6,426,220 and published PCT WO 02/36745; 5-O-Dimethoxymethyl-thymidine intermediate for 5-methylene dC amide, 5'-O-Dimethoxymethyl-2'-deoxy-5-methylcytidine intermediate for 5-methyl dC amide, 5'-O-Dimethoxymethyl-2'-deoxy-N4-benzoyl-5-methylcytidine penultimate intermediate for 5-methyl dC amide, [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-deoxy-N4-benzoyl-5-methylcytidin-3-O-yl]-2-cyaanoethyLN,N-diisopropylphosphoramide (5-methyl dC amide), 2'-Fluorodeoxyadenosine, 2'-Fluorodeoxyguanosine, 2'-Fluorouridine, 2'-Fluorodeoxyctydine, 2'-O-(2-Methoxethyl) modified amides, 2'-O-(2-methoxethyl)-5-methyluridine intermediate, 5'-O-DMT-2-O-(2-methoxethyl)-5-methyluridine penultimate intermediate, [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxethyl)-5-methyluridin-3-O-yl]-2-cyaanoethyLN,N-diisopropylphosphoramide (MOE T amide), 5'-O-Dimethoxymethyl-2'-O-(2-methoxethyl)-5-methylcytidine intermediate, 5'-O-Dimethoxymethyl-2'-O-(2-methoxethyl)-N4-benzoyl-5-methylcytidine penultimate intermediate, [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxethyl)-N4-benzoyl-5-methylcytidin-3-O-yl]-2-cyaanoethyLN,N-diisopropylphosphoramide (MOE S amide), [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxethyl)-N4-benzoyladenosin-3'-O-yl]-2-cyaanoethyl-N,N-diisopropylphosphoramide (MOE A amide), [5'-O-(4,4'-Dimethoxytriphenylmethyl)-2'-O-(2-methoxethyl)-N4-benzoyladenosin-3'-O-yl]-2-cyaanoethyl-N,N-diisopropylphosphoramide (MOE G amide), 2'-O-(Aminoethyl) nucleoside amides and 2'-O-(dimethylaminoethyl) nucleoside amides, 2'-O-(Dimethylaminoethoxy) nucleoside amides, 5'-O-tert-Butyldiphenylsilyl-2'-O-anhydro-5-methyluridine, 5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine, 2'-O-([2-phthalimidoclethyl]-5'-O-tetrahydropyrimidinyl)-5-methyluridine, 5'-O-tetrahydropyrimidinyl-2'-O-([2-formamidominoxy]ethyl)-5-methyluridine, 5'-O-tetrahydropyrimidinyl-2'-O-[N,N-dimethyliminoxyethyl]-5-methyluridine, 2'-O-(dimethylaminoxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(dimethylaminoxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(2-N,N-dimethylaminoxyethyl)-5-methyluridine-3'-O-[(2-cyaanoethyl)-N,N-diisopropylphosphoramide], 2'-O-(Aminoethoxy) nucleoside amides, N2-isobutyl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dime-thoxytrityl)guanosine-3'-O-[(2-cyaanoethyl)-N,N-diisopropylphosphoramide], 2'-O-dimethylaminoethoxy ethoxy (2'-DMAOE) nucleoside amides, 2'-O-[2-N,N-dimethylaminoxyethyl]-5-methyl uridine, 5'-O-dimethylaminoxyethyl-2'-O-[2-N,N-dimethylaminoxyethyl]-5-methyl uridine and 5'-O-Dimethoxymethyl-2'-O-[2-N,N-dimethylaminoxyethyl]-5-methyl uridine-3'-O-(cyaanoethyl-N,N-diisopropylphosphoramide).

**Example 2**

**Oligonucleotide and Oligonucleoside Synthesis**

[0108] The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may also 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 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 3,11,12-benzodithiole-3-one 1,1 -dioxide in anisotine for the oxidation of the phosphate linkages. The thiation reaction step time was increased to 180 sec and preceded by the normal capping step. After cleavage from the CPG column and deblocking in concentrated ammonium hydroxide at 55° C. (12-16 hr), the oligonucleotides were recovered by precipitating with 3 volumes of ethanol from a 1 M NH4OAc solution. Phosphite oligonucleotides are prepared as described in U.S. Pat. No. 5,508,270, herein incorporated by reference.

**[0110]** Alkyl phosphonate oligonucleotides are prepared as described in U.S. Pat. No. 4,469,863, herein incorporated by reference. 3'-Deoxy-3'-methylene phosphonate oligonucleotides are prepared as described in U.S. Pat. Nos. 5,610,289 or 5,625,050, herein incorporated by reference.

**[0111]** Phosphoramide oligonucleotides are prepared as described in U.S. Pat. No. 5,256,775 or U.S. Pat. No. 5,366,878, herein incorporated by reference.

**[0112]** Alkylphosphonothioate oligonucleotides are prepared as described in published PCT applications PCT/US94/06902 and PCT/US93/06976 (published as WO 94/17093 and WO 94/02499, respectively), herein incorporated by reference.
3′-Deoxy-3′-amino phosphoramidate oligonucleotides are prepared as described in U.S. Pat. No. 5,476,925, herein incorporated by reference.

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

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

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

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

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

Example 3

RNA Synthesis

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

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 nucleotide 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-cyanethylen-1, 1-dithiolate trihydrate (S2Na2) in DMF. The deprotection solution is washed from the solid support-bound oligonucleotide using water. The support is then treated with 40% methylamine in water for 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′-orthoeaster groups are the last protecting groups to be removed. The ethylene glycol monooacetate orthoester protecting group developed by Drhamacon 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′-ethoxy 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 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.


RNA antisense compounds (RNA oligonucleotides) of the present invention can be synthesized by the methods herein or purchased from Drhamacon 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, duplexes can be formed by combining 30 μM of each of the complementary strands of RNA oligonucleotides (50 μM RNA oligonucleotide solution) and 15 μl of 5× annealing buffer (100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, 2 mM magnesium acetate) followed by heating for 1 minute at 90°C, then 1 hour at 37°C. The resulting duplexed antisense compounds can be used in kits, assays, screens, or other methods to investigate the role of a target nucleic acid.
Example 4
Synthesis of Chimeric Oligonucleotides

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

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

Chimeric Phosphorothioate Oligonucleotides

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.

Chimeric Oligonucleotides

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 3H-1,2 benzothiadiole-3-one 1,1 dioxide (Beaucage Reagent) to generate the phosphorothioate internucleotide linkages for the center gap.

Example 5
Design and screening of duplexed antisense compounds targeting endothelial lipase

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 endothelial lipase. The nucleobase sequence of the antisense strand of the duplex comprises at least a portion of an oligonucleotide in Table 1. The ends of the strands may be modified by the addition of one or more natural or modified nucleobases to form an overhang. The sense strand of the dsRNA is then designed and synthesized as the complement of the antisense strand and may also contain modifications or additions to either terminus. For example, in one embodiment, both strands of the dsRNA duplex would be complementary over the central nucleobases, each having overhangs at one or both termini.

For example, a duplex comprising an antisense strand having the sequence CGAGAGCGCGAGGAG (SEQ ID NO: 280) and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

cagagagcgagggagTT Antisense Strand (SEQ ID NO: 281)

TTgctctgctgctgctg Complement (SEQ ID NO: 282)

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 aliquoted and diluted to a concentration of 50 μM. Once diluted, 30 ul of each strand is combined with 1 5ul 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 magnesium is 75 ul. 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 μM. This solution can be stored frozen (~20°C) and freeze-thawed up to times.

Once prepared, the duplexed antisense compounds are evaluated for their ability to modulate endothelial lipase expression.

When cells reached 80% confluence, they are treated with duplexed antisense compounds of the invention. For cells grown in 96-well plates, wells are washed once with 200 μl OPTI-MEM-1 reduced-serum medium (Gibco BRL) and then treated with 130 μl of OPTI-MEM-1 containing 12 μg/ml LIPOFECTIN (Gibco BRL) and the desired duplex antisense compound at a final concentration of 200 nM. After hours of treatment, the medium is replaced with fresh medium. Cells are harvested 16 hours after treatment, at which time RNA is isolated and target reduction measured by RT-PCR.
Example 6

Oligonucleotide Isolation

[0140] 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 NH₄OH with >3 volumes of ethanol. Synthesized oligonucleotides were analyzed by electrospray mass spectrometry (molecular weight determination) and by capillary gel electrophoresis and judged to be at least 70% full length material. The relative amounts of phosphorylthioate and phosphodiester linkages obtained in the synthesis was determined by the ratio of correct molecular weight relative to the -16 mm 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 Phosphoramidite chemistry on an automated synthesizer capable of assembling 96 sequences simultaneously in a 96-well format. Phosphodiester internucleotide linkages were afforded by oxidation with aqueous iodine. Phosphorothioate internucleotide linkages were generated by sulfuration utilizing 3,4-H,1,2 benzothiole-3-one 1,1 dioxide (Benacage Reagent) in anhydrous acetonitrile. Standard base-protected beta-cyanoethyl-diisopropyl phosphoramidites were purchased from commercial vendors (e.g. PI- 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-cyanoethyl-diisopropyl phosphoramidites.

[0142] Oligonucleotides were cleaved from support and deprotected with concentrated NH₄OH at elevated temperature (55-60°C) for 12-16 hours and the released product then dried in vacuo. The dried product was then re-suspended in sterile water to afford a master plate from which all analytical and test plate samples are then diluted utilizing robotic pipettors.

Example 8

Oligonucleotide Analysis—96-Well Plate Format

[0143] The concentration of oligonucleotide in each well was assessed by dilution of samples and UV absorption spectroscopy. The full-length integrity of the individual products was evaluated by capillary electrophoresis (CE) in either the 96-well format (Beckman P/ACE™ MDQ) or, for individually prepared samples, on a commercial CE apparatus (e.g., Beckman P/ACE™5000, ABI 270). Base and backbone composition was confirmed by mass analysis of the compounds utilizing electrospray-mass spectroscopy.

[0144] All assay test plates were diluted from the master plate using single and multi-channel robotic pipettors. Plates were judged to be acceptable if at least 85% of the compounds on the plate were at least 85% full length.

Example 9

Cell culture and oligonucleotide treatment

[0145] The effect of antisense compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the target nucleic acid is present at measurable levels. This can be routinely determined using, for example, PCR or Northern blot analysis. The following cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen. This can be readily determined by methods routine in the art, for example Northern blot analysis, ribonuclease protection assays, or RT-PCR.

T-24 cells:

[0146] The human transitional cell bladder carcinoma cell line T-24 was obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). T-24 cells were routinely cultured in complete McCoy’s 5A basal media (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, Calif.), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #353872) at a density of 7000 cells/well for use in RT-PCR analysis.

[0147] For Northern blotting or other analysis, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

A549 cells:

[0148] The human lung carcinoma cell line A549 was obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). A549 cells were routinely cultured in DMEM basal media (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, Calif.), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Invitrogen Corporation, Carlsbad, Calif.). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence.

NHDF cells:

[0149] 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 passages as recommended by the supplier.

HEK cells:

[0150] 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 passages as recommended by the supplier.
HuVEC cells: The human umbilical vein endothelial cell line HuVEC was obtained from the American Type Culture Collection (Manassas, Va.). HuVEC cells were routinely cultured in EBM (Clonetics Corporation Walkersville, MD) supplemented with SingleQuots supplements (Clonetics Corporation, Walkersville, MD). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence were maintained for up to passages. Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 10000 cells/well for use in RT-PCR analysis.

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.

Primary mouse hepatocytes

Primary mouse hepatocytes were prepared from CD-1 mice purchased from Charles River Labs. Primary mouse hepatocytes were routinely cultured in Hepatocyte Attachment Media (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco/Life Technologies, Gaithersburg, MD), 250 mM dexamethasone (Sigma), 10 mM bovine insulin (Sigma). Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 10000 cells/well for use in RT-PCR analysis.

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.

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 μL OPTI-MEM™-1 reduced-serum medium (Invitrogen Corporation, Carlsbad, Calif.) and then treated with 130 μL of OPTI-MEM™-1 containing 3.75 μg/mL LIPOFECTIN™ (Invitrogen Corporation, Carlsbad, Calif.) and the desired concentration of oligonucleotide. Cells are treated and data are obtained in triplicate. After 4-7 hours of treatment at 37°C, the medium was replaced with fresh medium. Cells were harvested 16-24 hours after oligonucleotide treatment.

The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control oligonucleotide is selected from either ISIS 13920 (TCCGT-CATCGCTTCCTCAAGG, SEQ ID NO: 1) which is targeted to human H-ras, or ISIS 18078, (GTGCCGCGCAGC-CGAAAAAT, 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, ATGCAT-TCTGCCCCAAAGGA, 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 unsuitable for oligonucleotide transfection experiments. The concentrations of antisense oligonucleotides used herein are from 50 nM to 300 nM.

Example 10

Analysis of oligonucleotide inhibition of endothelial lipase expression

Antisense modulation of endothelial lipase expression can be assayed in a variety of ways known in the art. For example, endothelial lipase 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 isolation is 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™7700, 7900, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, Calif. and used according to manufacturer’s instructions.

Protein levels of endothelial lipase 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 endothelial lipase can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aeric Corporation, Birmingham, Mich.), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art.

Example 11

Design of Phenotypic Assays and in vivo Studies for the use of Endothelial Lipase Inhibitors

Phenotypic Assays

Once endothelial lipase 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 endothelial lipase in health and disease. Representative phenotypic assays, which can be purchased from any one of several commercial vendors, include those for determining cell viability, cytotoxicity, proliferation or cell survival (Molecular Probes, Eugene, Oreg.; PerkinElmer, Boston, Mass.), protein-based assays including enzymatic assays (Panvera, LLC, Madison, Wis.;
In vivo Studies

The individual subjects of the in vivo studies described herein are warm-blooded vertebrate animals, which includes humans.

The clinical trial is subjected to rigorous controls to ensure that individuals are not unnecessarily put at risk and that they are fully informed about their role in the study.

To account for the psychological effects of receiving treatments, volunteers are randomly given placebo or endothelial lipase inhibitor. Furthermore, to prevent the doctors from being biased in treatments, they are not informed as to whether the medication they are administering is an endothelial lipase inhibitor or a placebo. Using this randomization approach, each volunteer has the same chance of being given either the new treatment or the placebo.

Volunteers receive either the endothelial lipase inhibitor or placebo for eight week period with biological parameters associated with the indicated disease state or condition being measured at the beginning (baseline measurements before any treatment), end (after the final treatment), and at regular intervals during the study period. Such measurements include the levels of nucleic acid molecules encoding endothelial lipase or endothelial lipase protein levels in body fluids, tissues or organs compared to pre-treatment levels. Other measurements include, but are not limited to, indices of the disease state or condition being treated, body weight, blood pressure; serum titers of pharmacologic indicators of disease or toxicity as well as ADME (absorption, distribution, metabolism and excretion) measurements.

Information recorded for each patient includes age (years), gender, height (cm), family history of disease state or condition (yes/no), motivation rating (some/moderate/great) and number and type of previous treatment regimens for the indicated disease or condition.

Volunteers taking part in this study are healthy adults (age 18 to 65 years) and roughly an equal number of males and females participate in the study. Volunteers with certain characteristics are equally distributed for placebo and endothelial lipase inhibitor treatment. In general, the volunteers treated with placebo have little or no response to treatment, whereas the volunteers treated with the endothelial lipase inhibitor show positive trends in their disease state or condition index at the conclusion of the study.

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 μL cold PBS. 60 μL lysis buffer (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 μL of lysis was transferred to Oligo d(T) coated 96-well plates (AGCT Inc., Irvine Calif.). Plates were incubated for 60 minutes at room temperature, washed 3 times with 200 μL of wash buffer (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 minutes. 60 μL of elution buffer (mM Tris-HCl pH 7.6), preheated to 70°C, was added to each well, the plate was incubated on a 50°C hot plate for minutes, and the eluate was then transferred to a fresh 96-well plate.

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

Total RNA Isolation

Total RNA was isolated using an RNEASY 96™ kit and buffers purchased from Qiagen Inc. (Valencia, Calif.) following the manufacturer’s recommended procedures. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well was washed with 200 μL cold PBS. 150 μL Buffer RLT was added to each well and the plate vigorously agitated for seconds. 150 μL of 70% ethanol was then added to each well and the contents mixed by pipetting three times up and down. The samples were then transferred to the RNEasy 96™ well plate attached to a QIAVAC™ manifold fitted with a waste collection tray and attached to a vacuum source. Vacuum was applied for 1 minute. 500 μL of Buffer AW1 was added to each well of the RNEASY 96™ plate and incubated for minutes and the vacuum was again applied for 1 minute. An additional 500
μL of Buffer RW 1 was added to each well of the RNEASY 96™ plate and the vacuum was applied for 2 minutes. 1 mL of Buffer RPE was then added to each well of the RNEASY 96™ plate and the vacuum was 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 QIAVACTM manifold and blotted dry on paper towels.

[0175] The plate was then re-attached to the QIAVACTM manifold fitted with a 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.

[0176] The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia Calif.). Essentially, after lysing of the cells on the culture plate, the plate is transferred to the robot deck where the pipetting, DNase treatment and elution steps are carried out.

Example 13

Real-time Quantitative PCR Analysis of Endothelial Lipase mRNA Levels

[0177] Quantitation of endothelial lipase mRNA levels was accomplished by real-time quantitative PCR using the ABI PRISM™ 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, Calif.) according to manufacturer’s instructions. This is a closed-tube, non-gel-based, fluorescence detection system which allows high-throughput quantitation of polymerase chain reaction (PCR) products in real-time. As opposed to standard PCR in which amplification products are quantitated after the PCR is completed, products in real-time quantitative PCR are quantitated as they accumulate. This is accomplished by including in the PCR reaction an oligonucleotide probe that anneals specifically between the forward and reverse PCR primers, and contains two fluorescent dyes. A reporter dye (e.g., FAM or JOE, obtained from either PE-Applied Biosystems, Foster City, Calif., Operon Technologies Inc., Alameda, Calif. or Integrated DNA Technologies Inc., Coralville, Iowa) is attached to the 5’ end of the probe and a quencher dye (e.g., TAMRA, obtained from either PE-Applied Biosystems, Foster City, Calif., Operon Technologies Inc., Alameda, Calif. or Integrated DNA Technologies Inc., Coralville, Iowa) is attached to the 3’end of the probe. When the probe and dyes are intact, reporter dye emission is quenched by the proximity of the 3’ quencher dye. During amplification, annealing of the probe to the target sequence creates a substrate that can be cleaved by the 5’exonuclease activity of Taq polymerase. During the extension phase of the PCR amplification cycle, cleavage of the probe by Taq polymerase releases the reporter dye from the remainder of the probe (and hence from the quencher moiety) and a sequence-specific fluorescent signal is generated. With each cycle, additional reporter dye molecules are cleaved from their respective probes, and the fluorescence intensity is monitored at regular intervals by laser optics built into the ABI PRISM™ Sequence Detection System. In each assay, a series of parallel reactions containing serial dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after antisense oligonucleotide treatment of test samples.

[0178] 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.

[0179] PCR reagents were obtained from Invitrogen Corporation, (Carlsbad, Calif.). RT-PCR reactions were carried out by adding μL PCR cocktail (2.5×PCR buffer minus MgCl₂, 6.6 mM MgCl₂, 375 μM 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, Units MuLV reverse transcriptase, and 2.5×ROX dye) to 96-well plates containing 30 μL total RNA solution (20-200 ng). The RT reaction was carried out by incubation for 30 minutes at 48°C. Following a minute incubation at 95°C, the PLATINUM® Taq, 40 cycles of a two-step PCR protocol were carried out at 95°C. For seconds (denaturation) followed by 60°C for 1.5 minutes (annealing/extension).

[0180] Gene target quantities obtained by real time RT-PCR are 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, Ore.), GAPDH expression is quantified by real time RT-PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantitated using RiboGreen™ RNA quantification reagent (Molecular Probes, Inc. Eugene, Ore.). Methods of RNA quantification by RiboGreen™ are taught in Jones, L.J., et al., (Analytical Biochemistry, 1998, 265, 368-374).

[0181] In this assay, 170 μL of RiboGreen™working reagent (RiboGreen™reagent diluted 1:350 in 10 mM Tris-HCl, 1 mM EDTA, pH 7.5) is pipetted into a 96-well plate containing 30 μL purified, cellular RNA. The plate is read in a CytoFluor 4000 (PE Applied Biosystems) with excitation at 485 nm and emission at 530 nm.

[0182] Probes and primers to human endothelial lipase were designed to hybridize to a human endothelial lipase
[0183] forward primer: CCGGACGGGAGCTGAATAT (SEQ ID NO: 5)

[0184] reverse primer: CAGTTTCGCTGGTITCC (SEQ ID NO: 6) and the PCR probe was: FAM-AGGGCTCACAGCACAG-GTAT (SEQ ID NO: 7) where FAM is the fluorescent dye and TAMRA is the quencher dye. For human GAPDH the PCR primers were:

[0186] forward primer: GAAGGTGGAAGGTGATGCT (SEQ ID NO:8)

[0187] reverse primer: GGAAGATGTGAGGTGATTTTC GGTCTGTCGTGCCTGAAAGAT (SEQ ID NO:9) and the PCR probe was: 5′JOE-CAAGGCTCTCCGTCTTCATAGCC-TAMRA 3′ (SEQ ID NO: 10) where JOE is the fluorescent reporter dye and TAMRA is the quencher dye.

[0188] Probes and primers to mouse endothelial lipase were designed to hybridize to a mouse endothelial lipase sequence, using published sequence information (GenBank accession number BC020991.1, incorporated herein as SEQ ID NO: 11). For mouse endothelial lipase the PCR primers were: forward primer: GCTGAAATGCCAACCAACACCTT (SEQ ID NO: 12) reverse primer: CAGGTAAGTCGCATCTTAAAGAGA (SEQ ID NO: 13) and the PCR probe was: FAM-CTTTGTCTACACTGAGGAAGTGTGGA-GTAMRA

[0189] (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: GGCCTAATCCGCCAGCT (SEQ ID NO: 15) reverse primer: GGGTCTGCTCTGGTACGAT (SEQ ID NO: 16) and the PCR probe was: 5′JOE-AAGGCGCAGAATGG-GGAGACTGCATCT-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 Endothelial Lipase mRNA Levels

[0190] Eighteen hours after antisense treatment, cell monolayers were washed twice with cold PBS and lysed in 1 mL RNAZOL™ (TEL-TEST “B” Inc., Friendswood, Tex.). Total RNA was prepared following manufacturer’s recommended protocols. Twenty micrograms of total RNA was fractionated by electrophoresis through 1.2% agarose gels containing 1% formaldehyde using a Mo. PS buffer system (AMRESCO, Inc. Solon, OH). RNA was transferred from the gel to HIBON™-N-nylon membranes (Amer- sham Pharmacia Biotech, Piscataway, N.J.) by overnight capillary transfer using a Northern/Southern Transfer buffer system (TEL-TEST “B” Inc., Friendswood, Tex.). RNA transfer was confirmed by UV visualization. Membranes were fixed by UV cross-linking using a STRATALINKER™ UV Crosslinker 2400 (Stratagene, Inc. La Jolla, Calif.) and then probed using QUICKHYBTM hybridization solution (Stratagene, La Jolla, Calif.) using manufacturer’s recommendations for stringent conditions.

[0191] To detect human endothelial lipase, a human endothelial lipase specific probe was prepared by PCR using the forward primer CCGGACGGGAGCTGAATAT (SEQ ID NO: 5) and the reverse primer CAGTTTCGCTGGTITCC (SEQ ID NO: 6). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, Calif.).

[0192] To detect mouse endothelial lipase, a mouse endothelial lipase specific probe was prepared by PCR using the forward primer GCTGAAATGCCAACCAACACCTT (SEQ ID NO: 12) and the reverse primer CAGGTAAGTCGCATCTTAAAGAGA (SEQ ID NO: 13). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for mouse glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, Calif.).

[0193] Hybridized membranes were visualized and quantitated using a PHOSPHORIMAGER™ and IMAGEQUANT™ Software V3.3 (Molecular Dynamics, Sunnyvale, Calif.). Data was normalized to GAPDH levels in untreated controls.

Example 15
Antisense Inhibition of Human Endothelial Lipase Expression by Chimeric Phosphorothioate Oligonucleotides Having 2′-Mo.E. Wings and a Deoxy Gap

[0194] In accordance with the present invention, a series of antisense compounds were designed to target different regions of the human endothelial lipase RNA, using published sequences (GenBank accession M₄, 006033.1, incorporated herein as SEQ ID NO: 4, a genomic sequence of endothelial lipase received by the complement of residues 3262-78294 of GenBank accession number NT₃, 025012.8, incorporated herein as SEQ ID NO: 18, GenBank accession number AW50414.1, the complement of which is incorporated herein as SEQ ID NO: 19, and GenBank accession number AF76039.1, the complement of which is incorporated herein as SEQ ID NO: 20). The compounds are shown in Table 1. “Target site” indicates the first (‘most’) nucleotide number on the particular target sequence to which the compound binds. All compounds in Table 1 are chimeric oligonucleotides ("gapers") nucleotides in length, composed of a central “gap” region consisting of ten 2′-deoxy-nucleotides, which is flanked on both sides (5′ and 3′ directions) by five-nucleotide “wings”. The wings are composed of 2′-methylthioethyl (2MOE)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 endothelial lipase mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from three experiments in which HuVEC cells were treated with oligonucleotides 259869-259946 (SEQ ID NOs: 21-98) of the present invention. The positive control for each data point is identified in the table by sequence ID number. If present, “N.D.” indicates “no data".
## TABLE 1

Inhibition of human endothelial lipase mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

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TABLE 1-continued

Inhibition of human endothelial lipase mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

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As shown in Table 1, SEQ ID NOs 21, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 65, 66, 67, 68, 69, 70, 72, 73, 74, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 92, 93 and 94 demonstrated at least 50% inhibition of human endothelial lipase expression in this assay and are therefore preferred. More preferred are SEQ ID NOs: 38, 68 and 84. The target regions to which these preferred sequences are complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 3. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 3 is the species in which each of the preferred target segments was found.

Example 16

Antisense Inhibition of Mouse Endothelial Lipase Expression by Chimeric Phosphorothioate Oligonucleotides Having 2'-MOE Wings and a Deoxy Gap.

[0196] In accordance with the present invention, a second series of antisense compounds were designed to target different regions of the mouse endothelial lipase RNA, using published sequences (GenBank accession number BC020991.1, incorporated herein as SEQ ID NO: 11, and GenBank accession number AF118768.1, incorporated herein as SEQ ID NO: 99). 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") nucleotides in length, composed of a central “gap” region consisting of ten 2'-deoxy-nucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide “wings". The wings are composed of 2'-methoxyethyl (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 endothelial lipase mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from three experiments in which mouse primary hepatocytes were treated with oligonucleotides 261160-261233 (SEQ ID NOs: 100-173) 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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Inhibition of mouse endothelial lipase mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

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Inhibition of mouse endothelial lipase mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

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As shown in Table 2, SEQ ID Nos 100, 101, 103, 104, 105, 107, 108, 109, 110, 111, 112, 113, 115, 116, 120, 122, 123, 124, 130, 131, 132, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 147, 148, 152, 154, 157, 158, 159, 160, 162, 163, 165, 166, 167, 168, 170 and 171 demonstrated at least 50% inhibition of mouse endothelial lipase expression in this experiment and are therefore preferred. More preferred are SEQ ID Nos: 104, 132 and 157. The target regions to which these preferred sequences are complementary are herein referred to as “preferred target segments” and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 3. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 1. “Target site” indicates the first (5’-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 3 is the species in which each of the preferred target segments was found.

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[0198] As these "preferred target segments" have been found by experimentation to be open to, and accessible for, hybridization with the antisense compounds of the present invention, one of skill in the art will recognize or be able to ascertain, using no more than routine experimentation, further embodiments of the invention that encompass other compounds that specifically hybridize to these preferred target segments and consequently inhibit the expression of endothelial lipase.

[0199] According to the present invention, antisense compounds include antisense oligomeric compounds, antisense oligonucleotides, ribozymes, external guide sequence (EGS) oligonucleotides, alternate spliceers, primers, probes, and other short oligomeric compounds which hybridize to at least a portion of the target nucleic acid.

**Example 17**

Western Blot Analysis of Endothelial Lipase Protein Levels

[0200] Western blot analysis (immunoblot analysis) is carried out using standard methods. Cells are harvested 16-20 h after oligonucleotide treatment, washed once with PBS, suspended in Laemmli buffer (100 ul/well), boiled for
minutes and loaded on a 16% SDS-PAGE gel. Gels are run for 1.5 hours at 150 V, and transferred to membrane for western blotting. Appropriate primary antibody directed to endothelial lipase is used, with a radiolabeled or fluorescently labeled secondary antibody directed against the primary antibody species. Bands are visualized using a PHOSPHORIMAGER™ (Molecular Dynamics, Sunnyvale Calif.).

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289

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<210> SEQ ID NO 23
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<400> SEQUENCE: 46
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<220> FEATURE:
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<400> SEQUENCE: 55

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<400> SEQUENCE: 58

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<400> SEQUENCE: 62

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<210> SEQ ID NO 63
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<400> SEQUENCE: 63

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<212> TYPE: DNA
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<400> SEQUENCE: 64

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<400> SEQUENCE: 65

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<210> SEQ ID NO 66
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 66

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<210> SEQ ID NO 67
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 67
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SEQ ID NO 68 LENGTH 20 TYPE DNA ORGANISM: Artificial Sequence FEATURE: OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 68
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SEQ ID NO 69 LENGTH 20 TYPE DNA ORGANISM: Artificial Sequence FEATURE: OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 69
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SEQ ID NO 70 LENGTH 20 TYPE DNA ORGANISM: Artificial Sequence FEATURE: OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 70
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SEQ ID NO 71 LENGTH 20 TYPE DNA ORGANISM: Artificial Sequence FEATURE: OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 71
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SEQ ID NO 72 LENGTH 20 TYPE DNA ORGANISM: Artificial Sequence FEATURE: OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 72
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SEQ ID NO 73 LENGTH 20 TYPE DNA ORGANISM: Artificial Sequence FEATURE: OTHER INFORMATION: Antisense Oligonucleotide

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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 75

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<400> SEQUENCE: 76

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<210> SEQ ID NO 77
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<220> FEATURE:
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<400> SEQUENCE: 77

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<210> SEQ ID NO 78
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<400> SEQUENCE: 78

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<400> SEQUENCE: 79

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<210> SEQ ID NO 80
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FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 80

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SEQ ID NO 81
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 81

cctccgaga tcagccgataa

SEQ ID NO 82
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 82

cctctctgct tgtgtcaca

SEQ ID NO 83
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 83

atcattcttc cctctctgct

SEQ ID NO 84
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 84

gggaagatac agatgaaaaac

SEQ ID NO 85
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 85

gaagtttaac atgtgatacaaa

SEQ ID NO 86
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 86
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<210> SEQ ID NO 87  
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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Antisense Oligonucleotide  
<400> SEQUENCE: 87  

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<210> SEQ ID NO 89  
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<210> SEQ ID NO 91  
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<210> SEQ ID NO 92  
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<223> OTHER INFORMATION: Antisense Oligonucleotide  
<400> SEQUENCE: 92  

ctagggac gccgttgaggg  

<210> SEQ ID NO 93  
<211> LENGTH: 20  
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<213> ORGANISM: Artificial Sequence  
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<400> SEQUENCE: 93  

taaggttaa cccctgctcag  

<210> SEQ ID NO 94  
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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Antisense Oligonucleotide  
<400> SEQUENCE: 94  

ttcctggttc ggatccagac  

<210> SEQ ID NO 95  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Antisense Oligonucleotide  
<400> SEQUENCE: 95  

tggagttgttt ggtgtttggc  

<210> SEQ ID NO 96  
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ctgggaaag ttcctggttc
<210> SEQ ID NO 93
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<223> OTHER INFORMATION: Antisense Oligonucleotide

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agcacttccttcgcttggg

<210> SEQ ID NO 94
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gtctagatgacgatgtaa

<210> SEQ ID NO 95
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gatcttgccagcagactgc

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tcttaaggaatgggttt

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atatacattagcctttcaaa

<210> SEQ ID NO 98
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agcacttcattatacatta

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aacgctgctg ttttcgggtc acacgctgca ggcctacccaa cttctcaggt tctcggcagct
  120
gttcccccgtc tccctccttg gcggagcaccc ggccgctgcca cttctagctt ctggaggttt
   180
tagtcgcttaca acacccacac aacccacac cacaacacgg cacaacacaa
   240
acgcgtgta gaggagggg cgggaggggg aagc ggt gca acac gct ttg ctg
Net Arg Asn Thr Val Phe Leu 1  5
  295
ctccggctctgccg gttgccgagagcc ggggccggagagct gccgccggagagct tccgccggagagct
Leu Gly Phe Trp Ser Val Tyr Cys Tyr Phe Pro Ala Asp Ser Ile Thr
  10  15  20
  343
acc ctg cgg ccc cag ggg tgg ctag cga gat gag cat cat aac ccc act
Thr Leu Arg Pro Glu Gly Ser Leu Arg Asp Glu His His Lys Pro Thr
  25  30  35
  391
ggg gta cca ggt acc ggc aga ccc tct gtg gct ttt aac atc cgc act
Gly Val Pro Ala Thr Ala Arg Pro Ser Val Ala Phe Aen Met Leu Ser Gly Asp Ser
  40  45  50  55
  439
tct aag gag cca gag cag gaa ggg tgt aat ctc tcc ctt ggt cag acg
Ser Lys Leu Leu Arg Asp Pro Glu Glu Glu Cys Aen Leu Leu Ser Leu Gly Asp Ser
  60  65  70
  487
aaa ctc tta gaa acc tgt ggc ttc acc atc aca gcc aac acc ttc tcc
Lys Leu Leu Leu Aen Asp Gly Phe Aen Met Thr Ala Lys Tyr Thr Phe
  75  80  85
  535
act att cat gga tgg acg atg gtc acc tgt ttc ggt gac tct cat
Ile Ile His Gly Trp Thr Met Ser Gly Met Phe Glu Ser Thr Leu His
  20  25  30
  583
aaa ctt gta tcc gcc ctc cag atg gac gaa gaa gag aac gat gct acc gtc cgt
Lys Leu Val Asp Ser Leu Aen Met Arg Gly Leu Aen Val Asn Val Val
  105  110  115
  631
gtg gtt gac tgg ctc ctc cag ctg cat cag tct acc gat gca gtt
Val Val Asp Trp Leu Pro Leu Ala His Glu Leu Tyr Thr Asp Ala Val
  120  125  130  135
  679
aat acc acc agg tgt gtt gga cag cag gta gct ggg atg ctt gac tgg
Aen Aen Thr Arg Val Gly Val Gly Leu Gly Met Leu Asp Trp
  140  145  150
  727
cgg cag gag gaa gaa ggc gct cag tcc ctt ggg acc gtt acc ctc cgg Val Leu
Glu Gin Glu Glu Glu Phe Ser Leu Gly Aen Val His Leu Ile Gly
  155  160  165
  775
tac acc ctt gga gca cac gtc gct gga tac gct ggc aac ttc gtt aac
Tyr Ser Leu Gly Aen Val Tyr Gly Asn Aen Gly Aen Phe Val Lys
  170  175  180
  823
ggg gac tgt ggc agg atc act gtt cgt cag ccc gcc ggt cct gcc gct
Gly Thr Val Gly Arg Ile Thr Gly Leu Asp Pro Gly Aen Gly Pro Met Phe
  185  190  195
  871
ggg ggg tgt gac aac aga agg ctc cgg gcc gac cgg gtt ccc cgg gtt ccc
Gly Val Gly Arg Ile Aen Arg Gly Arg Ser Pro Asp Ala Aen Asp Phe
  200  205  210  215
  919
gtt gat gtc ctc cat acc acg ctc cgg ctt ggc tgt gtc aac gtt
Val Asp Val Leu His Thr Tyr Thr Thr Thr Thr Thr Thr Thr Thr
  220  225  230
  967
att cgg gtt ctt gct gct cac att gac atc tct ccc aat ggc gtt gac
Ile Arg Met Pro Val Gly His His Asp Ile Tyr Pro Aen Gly Gly Asp
 1023 1015
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ttc cag cca ggc tgt gqa ttc aat gat gtc atc gqa tct ttt gca tat
Phe Glu Pro Gly Cys Gly Phe Asn Val Ile Gly Ser Ser Ala Tyr
       250 255 260

Gly Thr Ile Ser Glu Met Val Lys Cys Glu His Glu Arg Ala Val His
       265 270 275

cag ttc gca gac tcc agc ggc gaa gaa atg gaa aag cag gaa
Leu Phe Val Asp Ser Leu Val Glu Asp Asp Asp Ser Ser Arg
       280 285 290 295

cat tgc aca gac tcc agc cgc ttc aaa agg gga atc tgc ttc agc tgc
Gln Cys Thr Asp Ser Ser Arg Phe Lys Arg Gly Ile Cys Leu Ser Cys
       300 305 310

cgg aag aac cgt tgt ctt aac att ggc tac aac ggc aag aac cag
Arg Lys Asn Arg Cys Asn Asn Ile Lys Lys Tyr Asn Ala Lys Lys Met Arg
       315 320 325

Lys Lys Arg Asn Ser Lys Met Tyr Leu Lys Thr Arg Ala Gly Lys Met Pro
       330 335 340

ttc aat gtt tac cat tac cag ttt gac cag aag ttt tac ttc tac aat
Phe Lys Val Tyr His Ser Leu Cys Ser Asp Ser Ser Ser Ser Met Cys
       345 350 355

Aaa Ser Gly Asp Thr Glu Pro Thr Leu Tyr Ile Thr Leu Tyr Gly Ser
       360 365 370 375

aac gaa gac tcc cag aac ctt cag ctc tgg gas ata gtt gas aag att gag
Aaa Ala Asp Ser Glu Asn Asp Leu Pro Leu Lys Ile Glu
       380 385 390

ctg aat goc aca aac ctc ctt gtc tac act gag gag gag cag tgg
Leu Asn Ala Thr Asn Thr Phe Leu Val Tyr Thr Glu Asp Leu Gly
       395 400 405

Gat ctc tgg aag atg cga ctt acc tgg gag ggg gta ggc cat tcc tgg
Aaa Leu Lys Met Arg Leu Thr Trp Glu Gly Val Ala His Ser Trp
       410 415 420

Tgc aac ctt cgg aat ggt ttt cgg aac tac cgg tac tcc cac ccc agg aac
Cys Asn Leu Trp Asn Glu Phe Arg Asn Asn Tyr Leu Ser Pro Ser Ser Asn
       425 430 435

Ggc tcc cgg gag cag ctc cgg aac att cgt gtc aca aag tct ggg gaa
Pro Ser Arg Glu Leu Arg Ile Arg Ile Arg Val Lys Ser Gly Glu
       440 445 450 455

Acc cag cgc aag tgg aca tgc act cag aac aca aca gaa aat gag
Thr Glu Arg Lys Val Thr Phe Cys Thr Glu Asp Pro Pro Thr Lys Ser
       460 465 470

Atc tcc ctc ggc cag gag ctt ggg ttt cag aag tgc ggt
Ile Ser Pro Gly Glu Asp Glu Asp Asp Asp Ser Thr
645 650

Asn atg aag cag aag acc gat gcc ttc ctt gtt cag tgg cgc
Lys Met Lys Asn Asn Asp Ser Gly Val Thr His
655 660

Ggc cca cca aag tgc ccg ccc cat ctc cgg ccc ccc aag ctc tga
Glu Lys Glu Asn Gln Trp Asn Asp Ser Ser Ser Ser Ser Arg
670 675 680

Gtt tct ggt cgc cag gtc ctc cgg ccc ccc ctc ggc cca taag cca
Glu Asp Asp Asp Gln Val Val Arg Ser Ser Ser Glu Gln Glu
700 705 710

Tg ggc tct ggt ctc ctc cgg ccc ccc aag ctc ggc
Glu Gln Glu Val Val Arg Ser Ser Ser Arg Glu
715 720 725

Ggc cca cca aag tgc ccg ccc cat ctc cgg ccc ccc aag ctc tga
Glu Lys Glu Asn Gln Trp Asn Asp Ser Ser Ser Ser Ser Arg
670 675 680

Ggc cca cca aag tgc ccg ccc cat ctc cgg ccc ccc aag ctc tga
Glu Lys Glu Asn Gln Trp Asn Asp Ser Ser Ser Ser Ser Arg
670 675 680
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ggtaccttc ccttgctgta ggtgacact ggttggctc ascacaggc asccacggc 2137
ttgagacttg cccttgcttg aaggtggca ggtgcgtggc ctcactgac cttacgtgac 2197
agctcctggc tccgagcctg actcatgccc 2227

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 100

tcccagagc cgtgagaaag 20

<210> SEQ ID NO 101
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 101
gacctgga ggtggttagc 20

<210> SEQ ID NO 102
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 102
cctcagaga ctagagtagg 20

<210> SEQ ID NO 103
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 103
actssasct ccsagacta 20

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

<400> SEQUENCE: 104
cgtggtcgc atccttcgcc 20

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

<400> SEQUENCE: 105
cgtggtcgc atccttcgcc 20
<210> SEQ ID NO 106
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 106

tcatctcga gcacccctcg

<210> SEQ ID NO 107
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 107

tgatctcga gtgggttttt

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

<400> SEQUENCE: 108

tggagatgtt gaaagccaca

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

<400> SEQUENCE: 109

gtcaccaag gcagagttac

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

<400> SEQUENCE: 110

gcacaagtt ttaagagtt

<210> SEQ ID NO 111
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 111

gttatggact gcacccggtt

<210> SEQ ID NO 112
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 112
acccggtgt tatgcatcg

<211> SEQ ID NO: 113
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

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ccagtcagct atccagcota

<211> SEQ ID NO: 114
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 114
gttcacaagc gagaactttt

<211> SEQ ID NO: 115
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 115
cagctggtct ccaggtgctg

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

<400> SEQUENCE: 116
catccacana gttgcactcg

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

<400> SEQUENCE: 117
cagacatcc acsaagtctg

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

<400> SEQUENCE: 118

gtatgcagga cctccacaaaa

<210> SEQ ID NO 119
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 119
tgtaggtatg cagcacatcc

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

<400> SEQUENCE: 120
cacgtgtatg gtatgcagga

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

<400> SEQUENCE: 121
aaggacagcg ttaggtatg

<210> SEQ ID NO 122
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 122
agggacagcg ttaggtatg

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

<400> SEQUENCE: 123
ggtcagcagc aaggacagcg
ccastgtcga agccasagga

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

<400> SEQUENCE: 125
gatccast gctcaagcga

<210> SEQ ID NO 126
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 126
catccaga ccastgtcga

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

<400> SEQUENCE: 127
tagstgtca tgtgaccac

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

<400> SEQUENCE: 128
tggagataggtc castgtgga

<210> SEQ ID NO 129
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<212> TYPE: DNA
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<400> SEQUENCE: 129
cgccatggg atagatgtca

<210> SEQ ID NO 130
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

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<210> SEQ ID NO 131
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<212> TYPE: DNA
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<400> SEQUENCE: 131

aagaggtgt agcgtcgcct

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

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tgcacaagaa ggttaacgcc

<210> SEQ ID NO 133
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 133
gagaagctgc aagaggtgtct

<210> SEQ ID NO 134
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 134
caccagaagct gcacaagaa
tgcacaagaa
gagaagctgc aagaggtgtct

<210> SEQ ID NO 135
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 135
cagattcccc tttgaagcgc

<210> SEQ ID NO 136
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 136

ccaaatgttat tacacggtt

<210> SEQ ID NO 137
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 137

tgtagacttt cagctgtaa

<210> SEQ ID NO 138
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 138
tagagacca tgtgaacttt

<210> SEQ ID NO 139
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 139
ccactgtta tgtgaagaga

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

<400> SEQUENCE: 140
atccgagg gcagttctg

<210> SEQ ID NO 141
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 141
gttagacca gcagttgtt

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

<400> SEQUENCE: 142
gagatgcgcc aagtctctct

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

<400> SEQUENCE: 143
gtasgctcag ccotctctagac 20

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

<400> SEQUENCE: 144
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<210> SEQ ID NO: 145
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 145
ggastggct acococctcc

<210> SEQ ID NO: 146
<211> LENGTH: 20
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 146
cctacctcc agtttgcc

<210> SEQ ID NO: 147
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<210> SEQ ID NO: 148
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 148
caccttgaa accacagtc

<210> SEQ ID NO: 149
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 149
aaagggact gttttgtttt

<210> SEQ ID NO: 150
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<223> OTHER INFORMATION: Antisense Oligonucleotide

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aaagggact gttttgtttt
<211> LENGTH: 20  
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<213> ORGANISM: Artificial Sequence  
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<223> OTHER INFORMATION: Antisense Oligonucleotide  
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"ttggcctctc aggccagtt"  

<211> SEQ ID NO 151  
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<212> TYPE: DNA  
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"ccaggaagaa aagctcctgg"  

<211> SEQ ID NO 152  
<211> LENGTH: 20  
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<400> SEQUENCE: 152  

"tccagcaagaa cttcctcag"  

<211> SEQ ID NO 153  
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<223> OTHER INFORMATION: Antisense Oligonucleotide  
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<211> SEQ ID NO 154  
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<211> SEQ ID NO 155  
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<212> TYPE: DNA  
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"gctccacacac aagctgctggct"  

<211> SEQ ID NO 156  
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<223> OTHER INFORMATION: Antisense Oligonucleotide

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<400> SEQUENCE: 157

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taagttccag tgeggccagg

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gacctgctag taagttccag

<210> SEQ ID NO 164
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tctgctagtg atcaaggtgtg

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gccgcagcag tatgtagaac

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tcaaatcact aaaggtgtgc

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caggaaccc tgtctggtgc

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atgagttac agaaggaatt

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<210> SEQ ID NO 171
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<220> FEATURE:

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cgagtttggc ctctcagttgc 20

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gcactgactc castgcttc 20

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ttgagccccac cttttacgctc 20

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TYPE: DNA
ORGANISM: H. sapiens
FEATURE:

SEQUENCE: 211
gaggtatatag gatataagca

SEQ ID NO 212
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens
FEATURE:

SEQUENCE: 212
gaccotgagg ttttaaqtgq

SEQ ID NO 213
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens
FEATURE:

SEQUENCE: 213
agtgacgtgt tgtgtcacta

SEQ ID NO 214
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens
FEATURE:

SEQUENCE: 214
atagaagttt tagcatatgt

SEQ ID NO 215
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens
FEATURE:

SEQUENCE: 215
acccagctcct tttcatgttg

SEQ ID NO 216
LENGTH: 20
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FEATURE:

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<400> SEQUENCE: 217
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actagttagt ggtgcagcca

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atasacgaag gacactctgt

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agcggagag gaagaattgat

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<400> SEQUENCE: 232
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<210> SEQ ID NO 240
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<210> SEQ ID NO 241
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gcaatcaata aacaccagggt

<210> SEQ ID NO 244
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<220> FEATURE:

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cgatcgacg tttggtgatgg

<210> SEQ ID NO 247
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<220> FEATURE:

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<210> SEQ ID NO 252
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<400> SEQUENCE: 252
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aggagacctt ggcgatcttc 20

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cagggcatca cggacccttc

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cggacccttc cgacagcgtc

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cacccttgat ccttagcaga

<210> SEQ ID NO: 275
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gttctcata cctgctgagc

<210> SEQ ID NO: 276
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gaacctttt agtsgtttga

<210> SEQ ID NO: 277
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gaaccgaca ggtttcttgag

<210> SEQ ID NO: 278
<211> LENGTH: 20
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cgacactct ctgcatctgtg

<210> SEQ ID NO: 279
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What is claimed is:

1. A compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding endothelial lipase, wherein said compound specifically hybridizes with said nucleic acid molecule encoding endothelial lipase (SEQ ID NO: 4) and inhibits the expression of endothelial lipase.

2. The compound of claim 1 comprising 12 to 50 nucleobases in length.

3. The compound of claim 2 comprising 15 to 30 nucleobases in length.

4. The compound of claim 1 comprising an oligonucleotide.

5. The compound of claim 4 comprising an antisense oligonucleotide.

6. The compound of claim 4 comprising a DNA oligonucleotide.

7. The compound of claim 4 comprising an RNA oligonucleotide.

8. The compound of claim 4 comprising a chimeric oligonucleotide.

9. The compound of claim 4 wherein at least a portion of said compound hybridizes with RNA to form an oligonucleotide-RNA duplex.

10. The compound of claim 1 having at least 70% complementarity with a nucleic acid molecule encoding endothelial lipase (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of endothelial lipase.

11. The compound of claim 1 having at least 80% complementarity with a nucleic acid molecule encoding endothelial lipase (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of endothelial lipase.

12. The compound of claim 1 having at least 90% complementarity with a nucleic acid molecule encoding endothelial lipase (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of endothelial lipase.

13. The compound of claim 1 having at least 95% complementarity with a nucleic acid molecule encoding
endothelial lipase (SEQ ID NO: 4) said compound specifically hybridizing to and inhibiting the expression of endothelial lipase.

14. The compound of claim 1 having at least one modified internucleoside linkage, sugar moiety, or nucleobase.

15. The compound of claim 1 having at least one 2′-O-methoxyethyl sugar moiety.

16. The compound of claim 1 having at least one phosphorothioate internucleoside linkage.

17. The compound of claim 1 having at least one 5-methylcytosine.